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ON LEAD

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Prepared by

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PREFACE

The U.S. EPA is developing health-related guidance for lead that can be applied to a wide range of different media (soil/dust, air, diet). This report summarizes relevant information on health effects of lead and on lead exposure and presents a description of a proposed modeling approach for deriving media-specific criteria that can be tailored to specific exposure scenarios or cases. The rationale for using a modeling approach in place of more traditional risk assessment strategies such as Reference Dose is discussed. Much of the information presented in this report is taken from recent and more comprehensive Agency reviews, including the Air Quality Criteria Document (U.S. EPA, 1986a) and Review of the National Ambient Air Quality Standards for Lead (U.S. EPA, 1989a).

EXECUTIVE SUMMARY

This technical support document presents the rationale for an uptake/biokinetic modeling approach to developing health criteria for lead. Because of the apparent lack of a threshold for many of the noncancer effects of lead in infants and young children, coupled with multimedia exposure scenarios, meaningful oral and inhalation reference doses cannot be developed for lead. Blood lead levels, however, provide an important and useful index of risk because most toxicity endpoints associated with exposure to lead can be correlated with blood lead levels. The Uptake/Biokinetic Model described in this document, and described in greater detail in U.S. EPA (1989a), provides a method for predicting blood lead levels in populations exposed to lead in the air, diet, drinking water, indoor dust, soil and paint, thus making it possible to evaluate the effects of regulatory decisions concerning each medium on blood lead levels and potential health effects. This model, when integrated with the Industrial Soruce Complex for Dispersion model (U.S. EPA, 1986c), could be used to predict site-specific distributions of blood lead levels in populations in the vicinity of point sources.

Review of the available information concerning the toxicokinetics and health effects of lead in humans (and primates as well) leads to the conclusion that infants and young children are likely to be the most vulnerable segment of human populations exposed to lead and, therefore, should be the focus of risk assessment efforts. Studies in nonhuman primates provide strong empirical support for this conclusion. The relatively high vulnerability of infants and children results from a combination of several factors: 1) an apparent intrinsic sensitivity of developing organ systems

to lead; 2) behavioral characteristics that increase contact with lead from dust and soil (for example, mouthing behavior and pica); 3) various physiologic factors that result in greater deposition of airborne lead in the respiratory tract and greater absorption efficiency from the gastrointestinal tract in children than in adults; and 4) transplacental transfer of lead that establishes a lead burden in the infant before birth, thus increasing the risk associated with additional exposure during infancy and childhood.

A diverse set of undesirable effects has been correlated with blood lead levels in infants and children. Impaired or delayed mental and physical development, impaired heme biosynthesis and decreased serum vitamin D levels are correlated with blood lead levels across a range extending below 10 μg/dℓ. Although considerable controversy remains regarding the biological significance of some of the effects attributed to low lead exposure (e.g., blood lead levels below 10 μg/dℓ) remains, the weight of evidence is convincing that in infants and children, exposure-effect relationships extend to blood lead levels of 10-15 μg/dℓ and possibly lower.

The Uptake/Biokinetic Model provides a means for evaluating the relative contribution of various media to establishing blood lead levels. The results of such an analysis reveal that for areas having air lead levels that are typical for urban areas in the United States (e.g., 0.25 $\mu g/m^3$), and where the predominant lead source is assumed to be a point source (e.g., smelter/smoke stack), ingested lead will be the single largest uptake source in 2-year-old children; uptake from the respiratory tract will be almost insignificant. The model also predicts that ≈26% of the 2-year-old children living in such an environment and not exposed to lead-based paint but exposed to dietary lead levels as projected for the 1990 U.S. average

will have blood lead levels >10 µg/dℓ. Children exposed to lead paint can be expected to have considerably higher blood lead levels. The Uptake/ Biokinetic Model provides a useful and versatile method for exploring the potential impact of future regulatory decisions regarding lead levels in air, diet and soil.

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LIST OF ABBREVIATIONS

ALA-D	δ-aminolevulinic acid dehydrase
ALA-S	δ-aminolevulinic acid synthetase
bw	body weight
DNA	Deoxyribonucleic acid
EP	Erythroblast protoporphyrin
GCI	General Cognitive Index
G-R	Graham-Rosenbleth Behavioral Examinations for Newborns
GSD	Geometric standard deviation
KID	Kent infant development scale
LOAEL	Lowest-observed-adverse-effect level
MDI	Mental development index
MMAD	Mass median aerodynamic diameter
NBAS	Neonatal behavioral assessment scale
NOAEL	No-observed-adverse-effect level
OAQPS	Office of Air Quality Planning and Standards
PDI	Psychomotor development index
P5N	Pyrimidine-5'-nucleotidase
RfD	Reference dose
S.E.	Standard error
WPPSI	Wechsler preschool and primary scale of intelligence

1. INTRODUCTION

1.1. RFD METHODOLOGY AND RATIONALE FOR RFD DEPARTURE

The Agency has established the RfD for the purpose of quantitative risk assessment of noncarcinogenic chemicals. The RfD is an estimate with an uncertainty of one or several orders of magnitude of the highest continuous oral (mg/kg/day) or inhalation (mg/m^3) exposure that can occur over the human lifespan without the occurrence of adverse noncarcinogenic health effects (U.S. EPA, 1987, 1988a). In developing an RfD for a specific chemical, the best available scientific data on the health effects of the chemical is reviewed to identify the highest levels of exposure that are clearly not associated with adverse health effects in humans. Typically, the highest NOAEL is adjusted by an uncertainty factor to derive the RfD. The uncertainty factor reflects the degree of uncertainty associated with extrapolating the NOAEL identified from analysis of relevant human toxicological studies to the most sensitive fraction of the "healthy" human population.

When human toxicological data are inadequate to base conclusions regarding human NOAELs, NOAELs or LOAELs for the most sensitive animal species as defined by well-designed animal studies are utilized to derive the RfD. Doses or exposure levels are adjusted by conversion factors to account for allometric (e.g., body weight) and physiologic (e.g., breathing rates) differences between animal and humans. The adjusted NOAELs or LOAELs are then adjusted by an uncertainty factor to derive the RfD. Uncertainty factors for NOAELs derived from animal studies are larger than that for human NOAELs, reflecting the greater uncertainty associated with extrapolating dose-effect relationships from animals to humans. Consideration is given to uncertainties associated with extrapolations made from less

than lifetime exposures to lifetime exposures, from LOAELs to NOAELs and for differences in sensitivity between animals and humans.

The RfD approach has yielded useful quantitative estimates of toxic threshold for many chemicals, and thus, has been used as a "benchmark" on which to consider regulatory decisions in relation to potential impacts on human health; however, for reasons that are enumerated below it is inappropriate to derive an RfD for risk assessments related to environmental lead.

1.1.1. Absence of a Discernible Threshold for Health Effects of Lead. A critical assumption implicit to the RfD is the concept of threshold that a dose level exists below which adverse health effects will not occur. This assumption precludes developing RfDs based on effects for which thresholds have not been established from experimental or epidemiological data or for chemicals for which theoretical considerations suggest the absence of a threshold. Carcinogens fall into the latter category; for example, theoretical considerations suggest a finite probability that cancer could arise from the interactions of a single molecule of a mutagen with DNA (U.S. EPA, 1986a).

Analyses of correlations between blood lead levels and ALA-D activity, vitamin D and pyrimidine metabolism, neurobehavioral indices, growth and blood pressure indicate that the associations may persist through the lowest blood lead levels in the populations tested ($\leq$10-15 µg/dℓ). Thus, it is possible that if a threshold for the toxic effects of lead exists, it may lie within a range of blood lead levels <10-15 µg/dℓ; however, the data currently available are not sufficient to adequately define the dose-response relationship for many of the toxic effects of lead in populations having blood lead levels <10 µg/dℓ. Hence, it is not possible to

confidently identify a blood lead level below which no undesirable health effects would occur.

There is no widely accepted theoretical basis for the absence of a threshold for many of the health effects associated with lead exposure. Because the extensive experimental and human epidemiological studies published to date have failed to establish a threshold, it is prudent to assume, for regulatory purposes, that a threshold does not exist.

1.1.2. Multimedia Exposure Scenarios. Humans are exposed to lead from a variety of media; the relative contribution of each medium to total lead uptake changes with age and can vary in magnitude on a site-specific basis. Infants are born with a lead burden that primarily reflects the mother's past exposure and metabolic status during pregnancy. Infants and children are exposed to lead primarily from ingestion of food and beverages and from ingestion of nonfood sources by normal early mouthing behavior and pica. The impact of normal early mouthing behavior and pica will vary depending on the levels of lead in house dust, soil and paint, which in many but not all cases will be primarily related to air lead levels in the vicinity. Examples of exposure scenarios in which levels in soil and dust might not be related to air lead are situations involving contamination of soil and dust with leaded paint dusts and deposition of lead for stationery sources no longer in operation. Most adults, on the other hand, are exposed primarily from dietary (food and water) sources. Occupational exposures, however, may result in a significant contribution from the inhalation, dermal or ingestion route.

A viable risk assessment methodology for lead that is to be of any use in making regulatory decisions or for developing site-specific abatement

strategies must be flexible enough to incorporate site-specific information on exposure sources and demographic data. An ideal methodology would incorporate such information or would accept default values where data are not available and yield quantitative estimates of risk, in terms of predicted population distributions of blood lead levels.

RfD methodologies do not accommodate such considerations because they are basically route-specific risk assessments. The RfD can be defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risks of deleterious effects during a lifetime (U.S. EPA, 1988a). For example, an inhalation RfD is an estimate of the air concentration to which the most sensitive human populations can be exposed for a lifetime without appreciable risks to adverse effects and in the absence of exposures from other sources (e.g., the oral route). The latter assumption renders the inhalation RfD for lead relatively insignificant since inhaled lead contributes only a fraction of total lead uptake.

1.1.3. Blood Lead as the Primary Index of Exposure. The complex nature of lead exposure has not prevented advances in our understanding of dose-response relationships for lead in humans because many of the health effects of lead in humans appear to correlate with blood lead levels. Thus, blood lead (μg/dℓ) is a more appropriate "benchmark" for exposure than a level in air (mg/m^3) or an oral exposure level (mg/kg/day) would be.

Although it is unclear if thresholds exist for many lead exposure scenarios, significant concern is associated with blood lead levels. By estimating changes in blood lead level, one may estimate change in risk of experiencing health effects associated with the blood lead level. By examining changes in blood lead distribution, estimates of population risk

may be derived. It is possible to define critical ranges of blood lead levels and associated effects. In this way, blood lead levels can be used to define risk in a relative sense.

The nature of the effects associated with low level lead exposure are such that a scientific consensus regarding biological significance of many of the effects, such as neurobehavioral deficits associated with prenatal exposure, needs further evaluation. Therefore, it is not anticipated that critical ranges of blood lead as currently stated will have universal acceptance, nor is it reasonable to assume these levels should be universally applied to all exposure situations for risk assessment purposes. A given range of blood lead levels is likely to be associated with a given level of risk depending on other factors affecting the exposed population. For example, a given blood lead level may be undesirable in infants but of less significance to adults.

A useful risk assessment methodology for lead should provide a population distribution of blood lead levels and risk. The risk assessor can then evaluate the risks associated with such distributions and the potential benefits of parenting and abatement strategies given the definitions of critical blood lead levels for specific effects of lead, as well as the demographics and exposure sources for the population.

1.1.4. Predictive Biokinetic Models for Lead. It is currently feasible to utilize biokinetic models to provide predictions of blood lead levels that will result from any given range of route-independent lead uptake rates and vice-versa (U.S. EPA, 1989a). These models allow "benchmark" blood lead levels to be related quantitatively to route-independent uptake rates and can provide estimates of frequency distributions of blood lead levels associated with any given uptake rate.

1.1.5. Multimedia Exposure Analysis. Site-specific data or internationally consistent default assumptions regarding exposure scenarios and absorption efficiency for lead intake from various media can be incorporated into existing multimedia exposure analysis methods to yield estimates of the relative contributions of air, dietary and soil lead to any given estimated lead uptake (U.S. EPA, 1989a). Output from a multimedia analysis could be used to explore the possible outcomes of regulatory decisions and abatement strategies on the distribution of blood lead levels in relevant human populations. For example, a risk assessor could use these predictive models to estimate the effects of having soil lead at a specific exposure site on blood lead levels in 2-year-old children living in the vicinity of the site. This would be a far more useful risk management tool than a route-specific RfD.

In summary, the RfD approach is inappropriate for lead based on our current understanding of the dose-response relationship for the various effects of lead and multimedia nature of lead exposure. Multimedia exposure analysis coupled with predictive biokinetic models, however, provide a powerful tool for developing an alternative and more useful alternative risk assessment strategy for lead.

2. HEALTH EFFECTS SUMMARY

2.1. OVERVIEW

A significant amount of information regarding the toxicity of lead in humans has been gathered over the past 60 years. The symptoms of overt toxicity have been described and, for the most part, levels of lead in blood associated with frank toxicity have been established. There is little or no argument that excessive exposure resulting in lead levels extending upwards from 30-100 µg/dℓ is associated with a variety of overtly toxic effects on the peripheral and central nervous systems, kidneys and cardiovascular system.

In the most recent decade a shift has been seen in the emphasis of research objectives from a focus on overt toxicity to exploration of the more subtle physiologic, biochemical and neurobehavioral effects that may be associated with blood lead levels <30 µg/dℓ -- levels that can be anticipated to occur in a significant fraction of the general population. In particular, several factors have stimulated a renewed interest in exploring exposure-effect relationships in infants and children. These include (1) an appreciation that potentially significant lead burdens can be established in the fetus in utero; (2) that specific behavioral patterns of infants (4 weeks to 1 year) and children (1 to 5 years) facilitate intake of environmental lead; and (3) evidence that infants and children may be more sensitive and thus more vulnerable to some of the toxic effects associated with lead; several factors have stimulated renewed interest .

Research efforts during the last several years have greatly improved our understanding of the effects of low-level lead exposure. The advent of prospective epidemiological study designs that incorporate sensitive and

reproducible measures of physical and mental development has been a particularly important advancement in this area. While considerable concerns remain regarding the biological significance of some of the effects attributed to low lead exposure, the weight of evidence is convincing that in infants and children, exposure-effect relationships extend to blood lead levels of 10-15 μg/dℓ and possibly lower. Evaluations of the most recent data on blood pressure in adults suggest that exposure to lead may increase blood pressure. When viewed in relation to the number of children potentially exposed to environmental lead levels associated with blood lead levels of 10-15 μg/dℓ, even small increases in blood pressure may be of considerable public health significance.

The review that follows summarizes key issues relating to the toxicokinetics and health effects of lead in humans that will have to be considered in developing a responsible regulatory policy for lead. This review is not intended to be comprehensive but rather an overview of the various critical aspects of lead toxicity in humans, with more extensive discussions of recent information regarding effects associated with low levels (e.g., blood lead levels $\leq$10-15 μg/dℓ). Issues relating to the toxicokinetics of lead that are relevant to the validity of predictive models are also discussed. Discussions of overt toxicity have been abbreviated intentionally, and no attempt has been made to summarize the voluminous literature on laboratory animals.

An enormous amount of scientific literature regarding the health effects of lead in humans and animals has been published. Much of this information is contained in the Air Quality Criteria Document on Lead (U.S. EPA, 1986b), in subsequent addenda and related U.S. EPA documents (U.S. EPA, 1988a,b;

ATSDR/U.S. EPA, 1988) and in the recent ATSDR report to the U.S. Congress (ATSDR, 1988). The reader is referred to these documents for a more comprehensive treatment of the subjects and literature contained in this Chapter.

2.2. TOXICOKINETICS: ABSORPTION, DISTRIBUTION/BODY BURDEN, METABOLISM AND EXCRETION

Anthropogenic lead emissions to air consist primarily of lead in the inorganic form; therefore, the primary focus of this chapter is the toxicokinetics of inorganic lead. Organic lead compounds, notably tetraethyl, tetramethyl, triethyl and trimethyl lead, are also released into the air during the combustion of leaded gasoline. Lead alkyl compounds will generally be a minor component of lead released to air, but the toxicological significance can be appreciable under certain circumstances (e.g., children who "sniff" leaded gasoline). For this reason, the toxicokinetics of lead alkyls are also discussed in this chapter, with an emphasis on identifying important differences between the toxicokinetics of inorganic lead and lead alkyls.

2.2.1. Absorption. Oral absorption is quantitatively the most significant route of uptake of inorganic lead in most human populations; the exception is occupational exposures in which inhalation of airborne lead results in significant uptake. Oral absorption can result from ingestion of food, water and beverages as well as nonfood sources, such as soil and dust. Percutaneous absorption is not considered a significant route of absorption of inorganic lead. The rate and extent of absorption of inorganic lead is influenced by the physical and chemical properties of environmental lead. Factors such as particle size and solubility determine deposition patterns and dissolution rates within the entry portals of the

body, and may vary with specific exposure scenarios. Biological variation related to age and nutritional status will also influence absorption.

Alkyl lead compounds (e.g., triethyl, trimethyl, tetraethyl and tetramethyl lead) are more highly lipophilic than inorganic lead and are readily absorbed from the lung and skin. Extensive absorption from the gastrointestinal tract is predicted based on structural similarities between alkyl leads and alkyl tins.

2.2.1.1. ABSORPTION FROM THE RESPIRATORY TRACT — Inorganic lead in ambient air consists primarily of particulate aerosols, having a size distribution that is related to the characteristics and proximity to emission sources. While lead particles in most urban and rural air are in the sub-micron range, particle sizes in the vicinity of point sources can vary considerably (>30 to <2 μm) with distance from the source and meteorological patterns (Davidson and Osborne, 1984; Sledge, 1987). The number of inhaled lead particles of a given size range will vary with ambient air concentration and breathing rates. The latter can be expected to vary with age and physical activity.

The entry of inhaled lead into the systemic circulation involves the processes of deposition and absorption. Amounts and patterns of deposition of particulate aerosols in the respiratory tract are affected by the size of the inhaled particles, age-related factors that determine breathing patterns (e.g., nose breathing vs. mouth breathing), airway geometry and airstream velocity within the respiratory tract. In general, large particles (>2.5 μm) deposit in the nasopharyngeal regions of the human respiratory tract where high airstream velocities and airway geometry facilitate inertial impaction (Chamberlain et al., 1978; Chan and Lippmann, 1980). In the tracheobronchial and alveolar regions, where airstream velocities are lower,

processes such as sedimentation and interception become important for deposition of smaller particles (<2 μm). Diffusion and electrostatic precipitation become important for sub-micron particles reaching the alveolar region. Mouth breathing can be expected to increase aerosol deposition in the tracheobronchial and alveolar regions because the inhaled lead in the air bypasses the mucociliary obstruction of airflow to bypass the nasal region (Miller et al., 1986).

Absorption of lead from the respiratory tract is influenced by particle size and solubility as well as the pattern of regional deposition. Particles >2.5 μm in size that are deposited primarily in the ciliated airways of the nasopharyngeal and tracheobronchial regions of the respiratory tract can be transferred by mucociliary transport into the esophagus and subsequently absorbed from the gastrointestinal tract. Sneezing and coughing will clear a fraction of this lead from the body; only a fraction that is swallowed is absorbed in the gastrointestinal tract. Therefore, absorption of lead initially deposited in the upper respiratory tract will not be complete. Estimates for fractional absorption of large particles (>2.5 μm) deposited in the upper respiratory tract range from 40-50% (Kehoe, 1961a,b,c; Chamberlain and Heard, 1981).

Particles deposited in the alveolar region can enter the systemic circulation after dissolution in the respiratory tract or after ingestion phagocytic cells (e.g., macrophages). Available evidence indicates that lead particles deposited in the alveolar region of the respiratory tract are absorbed completely. Human autopsy results have shown that lead does not accumulate in the lung after repeated inhalation. This suggests complete absorption from the alveolar region (Barry, 1975; Gross et al., 1975). Chamberlain et al. (1978) exposed adult human subjects to ^{203}Pb in engine

exhaust, lead oxide or lead nitrate (<1 μm particle size) and observed that 90% of the deposited lead was cleared from the lung within 14 days. Morrow et al. (1980) reported 50% absorption of deposited lead inhaled as lead chloride or lead hydroxide (0.25±0.01 μg MMAD) within 14 hours. An analysis of the radioisotope dilution studies of Rabinowitz et al. (1977) in which adult human subjects were exposed daily to ambient air lead indicated that ≈90% of the deposited lead was absorbed daily (U.S. EPA, 1986b).

Quantitative analyses of the relationship between aerosol particle size and deposition in the human respiratory tract have been combined with information on size distributions of ambient air lead aerosols to estimate deposition and absorption efficiencies for inhaled lead in adults and children (U.S EPA, 1986b; Cohen, 1987). An example of estimates of average deposition and absorption for adults living in the vicinity of a stationary industrial source are provided in Table 2-1. Summing the fractional absorption values for each region of lung yields an estimate of 37.7% for the fractional absorption of inhaled lead in adults living in the vicinity of an industrial source. For some urban and rural atmospheres, where sub-micron particles dominate the airborne lead mass, fractional absorption is estimated closer to 15-30% (Cohen, 1987).

Breathing patterns, airflow velocity and airway geometry change with age, giving rise to age-related differences in particle deposition (Barltrop, 1972; James, 1978; Phalen et al., 1985). Depositions in various regions of the respiratory tract in children may be higher or lower than in adults, depending on particle size (Xu and Yu, 1986). For sub-micron particles, fractional deposition in 2-year-old children has been estimated as ≈1.5 times higher than that in adults (Xu and Yu, 1986). Estimates of regional and total fractional absorption in children can be calculated by

TABLE 2-1

Estimates of Regional Deposition and Absorption in the Adult Respiratory Tract of Ambient Air Lead Particles Found Near Point Sources[a]

Particle Size Range (μ)	% Ambient Lead Distribution Near Point Sources	Average Deposition Efficiency			Average Absorption Efficiency of Deposited Lead			% Absorption of Inhaled Lead		
		ALV[b]	T-B[c]	N-P[d]	ALV	T-B	N-P	ALV[e]	T-B	N-P
<1.0	12.5	0.15	0.05	0.003	1	0.4	0.4	1.9	0.25	0.015
1-2.5	12.5	0.25	0.10	0.20	1	0.4	0.4	3.1	0.5	1.0
2.5-15	20	0.20	0.25	0.40	1	0.4	0.4	4.0	2.0	3.2
15-30	40	ID	0.05	0.95	1	0.4	0.4	NC	0.8	15.2
>30	15	ID	ID	0.95	1	0.4	0.4	NC	NC	5.7

[a]Source: Cohen, 1987

[b]Alveolar

[c]Tracheobronchial

[d]Nasopharyngeal

[e]For <1.0 μm in alveolar region: 12.5 x 0.15 x 1 = 1.9%

ID = Insufficient deposition; NC = not calculated

making age-specific adjustments in regional fractional absorption for adults that are presented in Table 2-1. Adjustment factors for 2-year-old children, derived from the analysis of Xu and Yu (1986), are shown in Table 2-2. Summing the regional values yields an estimate of 42% for fractional absorption of inhaled lead in 2-year-old children living near a stationary industrial source. For general atmospheres in which sub-micron particles dominate the lead mass distribution, an adjustment factor of 1.5 can be applied to the estimated range of 15-30% for adults (Cohen, 1987).

Alkyl lead can occur in the atmosphere as a vapor or associated with atmospheric particulates (Harrison and Laxen, 1978). The retention and absorption of gaseous tetraethyl and tetramethyl lead has been examined in volunteers who inhaled ^{203}Pb-labeled tetraalkyl lead (Heard et al., 1979). Initial lung retention was 37 and 51% for tetraethyl and tetramethyl lead, respectively. Of these amounts, 40% of tetraethyl lead and 20% of tetramethyl lead was exhaled within 48 hours; the remaining fraction (tetraethyl, 60%; tetramethyl, 80%) was absorbed. Respiratory absorption of particulate alkyl lead has not been studied.

2.2.1.2. GASTROINTESTINAL ABSORPTION — The gastrointestinal tract is the primary site of absorption of lead in children and most adult populations, with the exception of those subject to occupational exposure (U.S. EPA, 1986b). Sources of input to the gastrointestinal tract include lead ingested in food and beverages and lead ingested in nonfood material such as dust, soil and lead-based paint. Nonfood materials are particularly important sources of lead intake in children because of normal mouthing behavior and pica. Inhaled lead that is deposited in the upper respiratory tract and subsequently swallowed also contributes to gastrointestinal input (U.S. EPA, 1986b, 1989a).

TABLE 2-2

Age Factor Adjustments for Calculating Deposition and Absorption of Ambient Air Lead Particles (Found Near Point Sources) in the Respiratory Tract of 2-Year-Old Children[a]

Particle Size Range (μm)	Age Factor Adjustment Deposition Efficiency			% Absorption of Inhaled Lead[b]		
	ALV[c]	T-B[d]	N-P[e]	ALV[f]	T-B	N-P
<1.0	1.5	1.5	1.5	2.9	0.4	0.02
1-2.5	1.3	1.7	1.5	4.0	0.9	1.5
2.5-15	0.5	1.4	2.0	2.0	2.8	6.4
15-30	ID	0.5	1.0	NC	0.4	15.2
>30	ID	ID	1.0	NC	NC	5.7

[a]Source: Xu and Yu, 1986

[b]Summing the regional values yields an estimate of 42% for fractional absorption of inhaled lead.

[c]Alveolar

[d]Tracheobronchial

[e]Nasopharyngeal

[f]For <1.0 μm in alveolar region: 1.9% (from Table 5-1) x 1.5 = 2.9%

ID = Insignificant deposition; NC = not calculated

Gastrointestinal absorption of lead varies with age, diet and nutritional status as well as the chemical species and particle size of the ingested lead. Dietary balance studies have yielded estimates ranging from 7-15% for gastrointestinal absorption in adults (Kehoe, 1961a,b,c; Chamberlain et al., 1978; Rabinowitz et al., 1980). Absorption may be 3-5 times greater if oral intake occurs during a period of fasting (Blake, 1976; Chamberlain et al., 1978; Heard and Chamberlain, 1982).

Gastrointestinal absorption of dietary lead is greater in infants and children than in adults. A balance study in infants of ages 2 weeks to 2 years, yielded estimates of 42% for children with dietary intakes of $\geq$5 μg Pb/kg bw. Lower dietary intakes were associated with highly variable absorption (Ziegler et al., 1978). A study conducted with infants and children of ages 2 months to 8 years (daily intake, 10 μg Pb/kg bw) yielded estimates of 53% for gastrointestinal absorption (Alexander et al., 1973).

Gastrointestinal absorption of lead is affected by a variety of dietary and nutritional factors. The results of numerous studies of the effects of diet on lead absorption and retention in humans and animals are summarized in the Air Quality Criteria Document for Lead (U.S. EPA, 1986b). Based on the results of these studies, it can be predicted that increased gastrointestinal absorption of lead may occur in populations consuming diets low or deficient in calcium, iron, phosphate, copper, vitamin D, protein or fiber, or diets having a lipid content. This suggests that individuals with poor nutritional status may absorb more lead from environmental sources.

Gastrointestinal absorption of lead alkyls is not likely to be an important route of uptake of environmental lead because of the relatively

high volatility of lead alkyls. The exception would be in situations where people are ingesting groundwater contaminated with tetraethyl lead. The acidic environment of the stomach will promote the conversion of tetraethyl and tetramethyl lead to the corresponding trialkyl derivatives (U.S. EPA, 1986b). Although the absorption of trialkyl leads has not been studied, extensive absorption is predicted based on information regarding the gastrointestinal absorption of the structurally similar Group IV analogs, triethyl and trimethyl tins (Barnes and Stoner, 1958).

2.2.1.3. PERCUTANEOUS ABSORPTION — Inorganic lead is not readily absorbed through the skin. Values of 0-0.3% of administered dose were reported for humans exposed to dermal applications of cosmetic preparations containing lead acetate. The highest absorption was observed when the skin was scratched (Moore et al., 1980). Thus, percutaneous absorption is not considered to be a significant route of uptake of inorganic lead in humans, relative to gastrointestinal and respiratory tract absorption. This contrasts with lead alkyls that are absorbed through the skin to a greater extent than inorganic lead.

Tetraethyl and tetramethyl lead are rapidly absorbed through the skin in rabbits and rats (Kehoe and Thamann, 1931; Laug and Kunze, 1948). Evaporation can be expected to compete with absorption for removal from skin; however, even under conditions in which evaporation was allowed to occur, percutaneous absorption of tetraethyl lead was 6.5% (Laug and Kunze, 1948).

2.2.2. Tissue Distribution of Lead. Mineralized tissues (e.g., bone and teeth) are the single largest pool for absorbed lead, accounting for ≈95% of total lead burden in adults and slightly less in children (Barry, 1975, 1981). Lead not contained in mineralized tissue is distributed in soft tissues, primarily blood, liver and kidneys. Small amounts accumulated in

other soft tissues such as brain, although not quantitatively significant to the overall distribution of the body burden, are of considerable toxicological importance. Lead readily transfers across the placenta and distributes to fetal tissues (Horiuchi et al., 1959; Barltrop, 1959; Bellinger et al., 1987a; Dietrich et al., 1987).

Elimination half-lives for lead in soft tissues are relatively short (weeks). Estimates of elimination half-lives for lead in blood in adults range from 15-35 days (Chamberlain et al., 1975, 1978; Rabinowitz et al., 1973, 1976). Studies using adult and juvenile baboons indicate that elimination half-life for kidney and liver, and probably other soft tissues, are similar to that for blood (Harley and Kneip, 1985). Because of the relatively short half-life, accumulation in soft tissue does not continue over the lifetime exposure (Schroeder and Tipton, 1968; Barry and Mossman, 1970; Barry, 1975, 1981). The exception is the kidney cortex, in which lead can accumulate in nuclear inclusion bodies in uremic or hypertensive persons (Indraprasit et al., 1974). Abrupt increases in blood lead levels can be expected to result in new higher steady-state levels in blood and other soft tissues within 60-120 days (Tola et al., 1973; Griffin et al., 1975); however, following a decrease in uptake, lead in bone and other tissue stores slowly redistri- butes to blood. Thus, more time may be required to achieve a new steady- state blood level after uptake decreases, depending on the level and duration of prior exposure (Rabinowitz et al., 1977; O'Flaherty et al., 1982; Gross, 1981).

Elimination half-lives in children and adults for mineralized tissue, such as bone, are considerably longer than for soft tissues (years). As a result, a decade or more of constant exposure is required to achieve a

steady state in bone (Rabinowitz et al., 1976; Holtzman, 1978). Bone lead can provide a store for continuous release of lead to soft tissues in the event that uptake decreases (O'Flaherty et al., 1982). Metabolic stress resulting in increased bone turnover or demineralization, such as that which normally occurs during pregnancy or aging, may accelerate release of lead from bone (Manton, 1985; Drasch et al., 1987; Zaric et al., 1987; Silbergeld et al., 1988). Therefore, the potential exists for a portion of the bone lead burden of the parent to be transferred to the fetus during pregnancy.

Limited studies on the subcellular distribution of lead in humans and more extensive studies using animals have shown that lead accumulates in the nucleus and mitochondria (Goyer et al., 1970; Cramer et al., 1974; Flood et al., 1988). Approximately 75% of lead in erythrocytes is bound to hemoglobin and other intracellular proteins; most of the remaining 25% is thought to be associated with low molecular weight ligands such as amino acids and nonprotein thiols (Bruenger et al., 1973; Raghaven and Gonick, 1977; Everson and Patterson, 1980; Ong and Lee, 1980; DeSilva, 1981). Fetal hemoglobin has a greater affinity for lead than adult hemoglobin (Ong and Lee, 1980). The fraction of blood lead in serum increases with increasing blood lead levels >40-50 μg/dℓ, and may approach 2% of whole blood lead at blood lead levels >100 μg/dℓ (Manton and Cook, 1984).

Tissue distribution of lead after exposure to tetraethyl or tetramethyl lead primarily reflects the distribution of the dealkylation products, trialkyl, dialkyl and inorganic lead (Cremer, 1959; Cremer and Calloway, 1961; Stevens et al., 1960). In blood, partitioning of lead between the plasma and erythrocyte fractions varies with animal species and metabolism. Triethyl and trimethyl lead bind tightly to rat hemoglobin and concentrates in erythrocytes in this species. Human erythrocytes have a relatively low

affinity for triethyl and trimethyl lead (Byington et al., 1980). After exposure to tetraalkyl leads, trialkyl leads are found in the plasma (Boeckx et al., 1977; Goldings and Stewart, 1982). After humans inhale ^{203}Pb-labeled tetraethyl and tetramethyl lead, lead distributes in whole blood primarily in the plasma fraction (Heard et al., 1979). Clearance from whole blood is nearly complete within 10 hours and is followed by the reappearance of lead in erythrocytes. The shift in distribution of lead from the plasma to the erythrocyte fraction of whole blood may reflect dealkylation in tissues and the appearance of dialkyl or inorganic lead in the blood, which has a higher affinity for erythrocytes than do tetraalkyl or trialkyl leads.

Lead distributes to a variety of tissues after exposure to lead alkyls. Levels of lead are highest in liver followed by kidney and brain in humans that have been exposed to tetraethyl and tetramethyl lead (Bolanowska et al., 1967; Grandjean and Nielson, 1979). The kinetics of elimination of triethyl lead in humans has been described by a two-compartment model having half-lives of 35 and 100 days (Yamamura et al., 1975).

2.2.2.1. METABOLISM OF LEAD — Metabolism of inorganic lead consists primarily of reversible ligand reactions including the formation of complexes with amino acids and nonprotein thiols and binding to various cellular proteins (Bruenger et al., 1973; Raghaven and Gonick, 1977; Everson and Patterson, 1980; Ong and Lee, 1980; DeSilva, 1981).

Tetraethyl and tetramethyl lead undergo oxidative dealkylation to the corresponding trialkyl derivatives, which are thought to be the neurotoxic forms of these compounds. Dealkylation of tetraalkyl lead occurs in a variety of species, including humans (U.S. EPA, 1986b). The conversion from tetraalkyl to trialkyl lead is catalyzed by a cytochrome P-450 dependent monooxygenase system in liver microsomes (Kimmel et al., 1977) and occurs

rapidly. The maximum rate of conversion of tetraethyl lead to triethyl lead was estimated to be 200 µg/hour/g liver in rats (Cremer, 1959). Complete dealkylation to inorganic lead has been shown to occur in a variety of species, including humans. The formation of inorganic lead from tetraalkyl leads may account for the hematological effects associated with chronic exposure to alkyl leads, including exposure of children who inhale leaded gasoline.

2.2.2.2. EXCRETION OF LEAD — Lead that is absorbed from all routes is excreted in the feces by biliary secretion, and in the urine, in ≈1:2 proportions (Chamberlain et al., 1978). Approximately 50-60% of absorbed lead is excreted with a half-life of 30-50 days. The remaining fraction is distributed to tissues, primarily bone, and is excreted with a half-life of several years (Kehoe, 1961a,b,c; Rabinowitz et al., 1976; Chamberlain et al., 1978).

Lead is excreted primarily in the urine as dealkylated products after exposure to lead alkyls. The chemical form that appears in urine may vary with animal species. In humans exposed to tetraethyl lead, ≈10% of urinary lead is in the form of triethyl lead (U.S. EPA, 1986b).

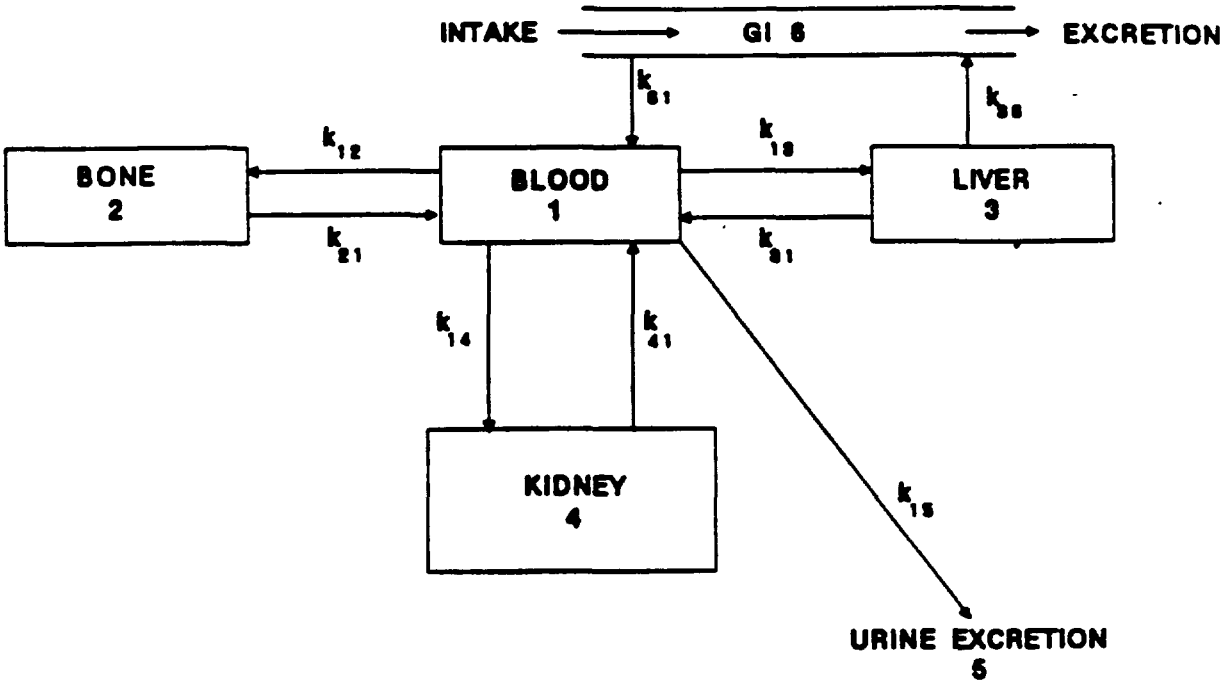
2.2.2.3. BIOKINETIC MODELS — Several mathematical models have been developed to describe uptake, distribution and excretion of lead (Rabinowitz et al., 1976; Kneip et al., 1983; Marcus, 1985a,b,c). These models are important for risk assessment because they provide a basis for making predictions about levels of lead in various physiological compartments that would be associated with a given rate of uptake or exposure level. The various models that have been suggested differ in complexity with respect to the number of physiological compartments described, and assumptions regarding kinetics of exchange between compartments.

The model proposed by Rabinowitz et al. (1976) was based on the results of radioisotope tracer studies using volunteers. The model specified three physiological compartments for lead distribution: blood, soft tissue (other than blood) and bone.

The model proposed by Kneip et al. (1983) was based on kinetic constants derived from single injection studies and chronic oral exposures in adult and juvenile baboons (Kneip et al., 1983). The model was subsequently modified to incorporate age-related changes in metabolism and physiology in humans (Harley and Kneip, 1985). Figure 2-1 illustrates the model for 2-year-old children. Three major tissue compartments that exchange with the blood compartment are defined in the model: bone, liver, kidney and gastrointestinal tract. First-order rate constants for exchanges between blood and tissues are defined along with rate constants for transfers of lead from liver to the gastrointestinal tract (e.g., biliary secretion) and from blood into the urine.

Marcus (1985a,b,c) proposed a more elaborate model based on measurements obtained from a volunteer subject who ingested lead (DeSilva, 1981). In addition to soft and hard tissue compartments, the model includes an expanded blood compartment containing four subcompartments: "deep" and "shallow" pools in the erythrocyte, and a diffusible and protein bound pool in plasma. A unique feature of this model is that it addresses nonlinearities in the relationship between lead in blood and lead in plasma.

Of the various models that have been proposed, the Harley and Kneip (1985) model is unique in that it yields age-specific predictions for lead levels in the major tissues given specified rates of lead uptake into blood. This makes it particularly suitable for applications to risk assessments in which predictions concerning the distributions of blood lead levels among



$k_{12} = 0.13$
$k_{21} = 6.11 \times 10^{-4}$
$k_{13} = 0.07$
$k_{31} = 0.03$
$k_{14} = 0.02$
$k_{41} = 0.07$
$k_{15} = 0.08$
$k_{56} = 0.14$
$k_{61} = 0.30$

FIGURE 2-1

Schematic Model of Lead Metabolism in 2-Year-Old Children, with Compartmental Transfer Rate Constants

various age groups within exposed populations are essential. Furthermore, because lead uptake is a primary input to the model, the model can be used in conjunction with multimedia uptake models to predict blood lead levels associated with exposure levels in various environmental media. The Harley and Kneip (1985) model has been successfully validated using available human experimental and autopsy data (U.S. EPA, 1989a). Because this model was developed specifically to predict tissue lead concentrations over time in young children with continuous lead uptake, the model was selected by the Office of Air Quality Planning and Standards (U.S. EPA, 1989a) for predicting blood lead levels that would be associated with lead uptakes derived from the integrated lead uptake methodologies described in Chapter 4 of this document. A more complete discussion of the integration of the Harley and Kneip (1985) model with lead uptake models is presented in Chapter 4.

2.3. SYSTEMIC AND TARGET ORGAN TOXICITY

2.3.1. Neurobehavioral Toxicity.

2.3.1.1. LEAD NEUROTOXICITY IN ADULTS — Severe lead neurotoxicity is characterized by overt symptoms of irritability, shortening of attention span, headache, muscular tremor, peripheral neuropathy, abdominal pain, loss of memory and hallucinations. Delirium, convulsions, paralysis and death can also occur. In adults, some of these overt symptoms may become apparent at blood lead levels in the range of 40-60 µg/dℓ (U.S. EPA, 1986b).

Nonovert symptoms of neurotoxicity that have been associated with lead exposure in adults include impaired performance on psychomotor tests, decreased nerve conduction velocity and impaired cognitive function (e.g., IQ). Blood lead levels associated with these effects range upwards from 30 µg/dℓ (U.S. EPA, 1986b).

2.3.1.2. LEAD NEUROTOXICITY IN CHILDREN — Symptoms of overt neurotoxicity in children are similar to those that are observed in adults. Based on a review of available data, U.S. EPA (1986b) concluded that overt symptoms can be anticipated in the most sensitive children having blood lead levels ≥20 μg/dℓ.

Nonovert symptoms of neurotoxicity that have been reported in children include impairments or abnormalities in psychomotor and cognitive function. Numerous studies have examined psychomotor and cognitive function of "high-risk" populations of children. Such populations are those typically identified from clinical lead screening programs as having elevated blood lead levels, children with previous histories of lead encephalopathy or paint pica and children with possible occupational exposure (e.g., lead pottery manufacture). Based on an extensive review of these data, the Agency concluded that, although the evidence is not conclusive, severe psychomotor and cognitive deficits appear to be associated with blood lead levels at the range of ≥40-60 μg/dℓ (U.S. EPA, 1986b).

Studies of general pediatric populations (e.g., infants and children with no known history of excessive exposure or toxicity) provide information about subtle neurological effects in children with lower blood lead levels and body burdens than the studies of high-risk populations. An extensive Agency review of these studies concluded the following (U.S. EPA, 1986b):

> 1) they are suggestive of relatively minimal (if any) effects on IQ in general populations, especially in comparison with the much larger effects of other factors (e.g., social variables), at the exposure levels evaluated in these studies (blood lead levels mainly in the 15-30 μg/dℓ range); and 2) they are not incompatible with findings of significant lead effects on IQ at average blood lead levels (≥30 μg/dℓ).

Several large-scale studies have been reported since completion of the above analysis (U.S. EPA, 1986b) that indicate effects on mental development and cognitive ability associated with blood lead levels ≤10-15 μg/dℓ. A brief discussion of the key prospective studies of mental development in infants and young children is presented in Section 2.4.1. of this document.

Two recent cross-sectional studies on cognitive ability in school-aged children have been reported. As shown in Figure 2-2, an inverse linear association between Stanford-Binet IQ scores and contemporary blood lead levels was seen over the entire range of 6-47 μg/dℓ in a study of uniformly low socioeconomic status black children, 3-7 years old (Hawk et al., 1986; Schroeder and Hawk, 1987). A study of 6- to 9-year-old children in Edinburgh, Scotland, also indicated a negative linear correlation between blood lead and scores on tests of cognitive ability (Fulton et al., 1987). The correlation extended across a range of 5-22 μg/dℓ mean blood lead levels (Figure 2-3).

A more recent study examined data on nerve conduction velocity in children living in the vicinity of a lead smelter (Schwartz et al., 1988). Based on "hockey stick," quadratic and logistic regression analyses of the maximal nerve conduction velocity and blood lead level data in 202 children (ages 5-9 years), a threshold for decreased maximal nerve conduction was estimated to be within the range of 20-30 μg/dℓ (Figure 2-4). Animal studies provide the opportunity to examine neurobehavioral effects of lead under controlled conditions, which are not possible in human studies. Recent data with nonhuman primates provide strong support for high sensitivity to lead in newborns (Levin et al., 1988; Bushnell and Bowman, 1979a,b; Gilbert and Rice, 1987).

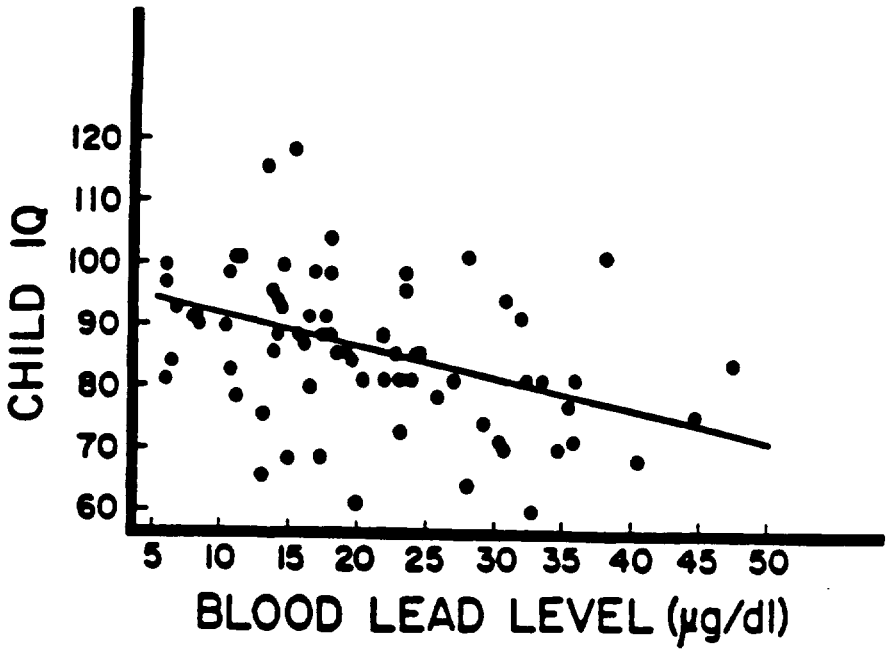


FIGURE 2-2

Child IQ as a Function of Blood Lead Level in Children 3-7 Years Old

Source: Schroeder and Hawk, 1987

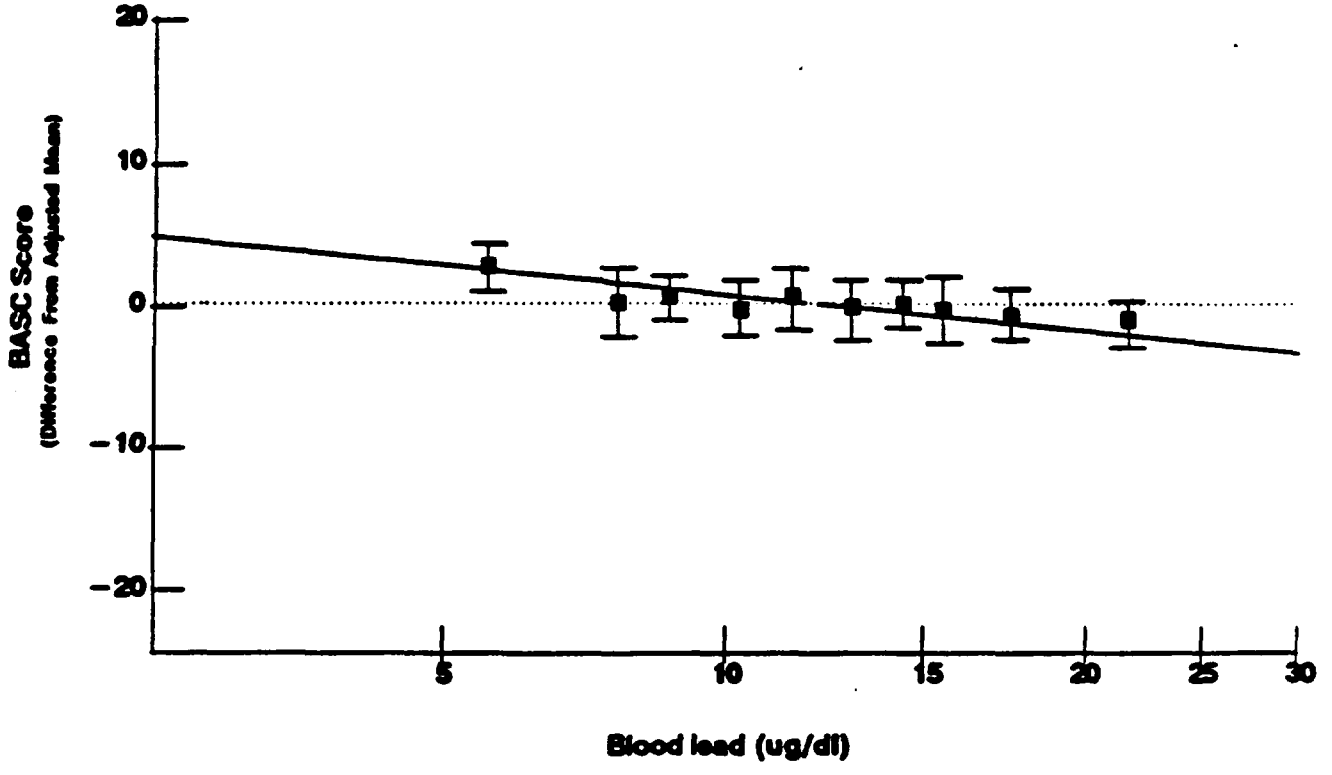


FIGURE 2-3

British Ability Scales Combined Score (BASC, Means and 95% Confidence Intervals) as a Function of Blood Lead Level in Children 6-9 Years Old

Source: Fulton et al., 1987

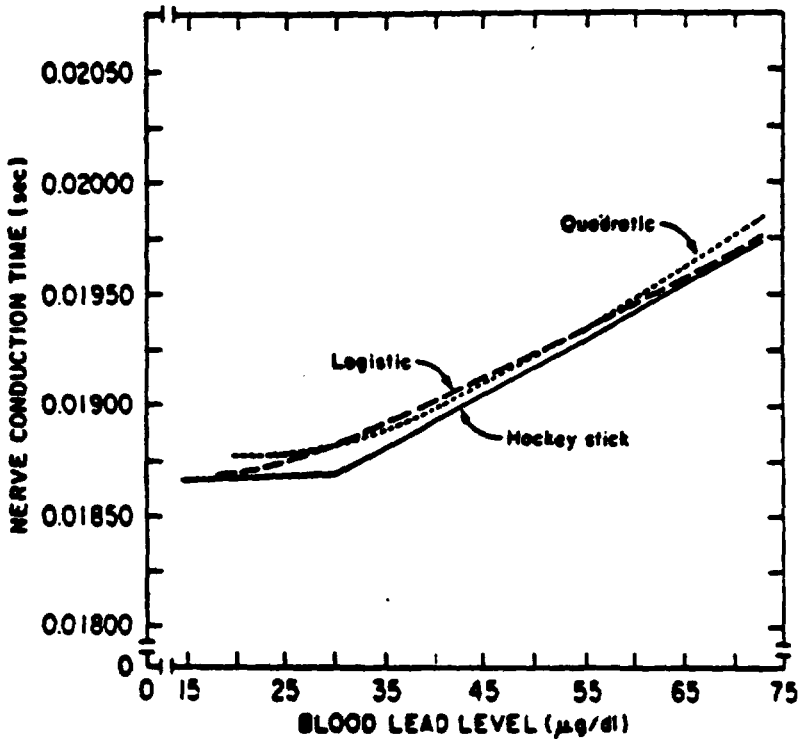


FIGURE 2-4

Maximal Nerve Conduction Time as a Function of Blood Lead Level in Children 5-9 Years Old. (Data from 202 children are fit to logistic, quadratic and "Hockey Stick" models)

Source: Schwartz et al., 1988

2.3.2. Effects of Lead on Heme Biosynthesis and Erythropoiesis. The process of heme biosynthesis is outlined in Figure 2-5. Lead interferes with heme biosynthesis by decreasing the activity of the enzymes ALA-D and ferrochelatase. Increased activity of the enzyme ALA-S may also occur as a secondary effect of feedback regulation. While these effects can be most readily demonstrated in erythroblast, there is evidence that indicates lead may derange heme biosynthesis in other tissues, including the central nervous system (Moore and Goldberg 1985; Silbergeld, 1987). Thus, altered heme metabolism in erythroblasts may be indicative of similar disruptions in other erythropoietic tissues that may contribute to more severe systemic or neurological effects.

Significant impairment of hemoglobin synthesis occurs in adults at relatively high blood levels. The threshold for a decrease in blood hemoglobin in adults and children is achieved at a blood lead level of 50 µg/dl (Meredith et al., 1977; Fischbein, 1977; Alvares et al., 1975). Frank anemia in adults has been associated with levels >80 µg/dl (Tola et al., 1973; Grandjean, 1979; Lilis et al., 1978; Wada et al., 1973; Baker et al., 1979). The relationship between blood lead levels and heme biosynthesis in other sensitive tissues, such as central nervous or cardiovascular tissues, has not been characterized.

The effects of lead on erythroblast heme biosynthesis can be detected from measurements of the activity of erythrocyte ALA-D or levels of EP, a substrate for ferrochelatase. Erythroblast ALA-D activity is inversely correlated with blood lead level in infants, children and adults (Figure 2-6); the correlation persists when examined across a range of blood lead levels $\leq$3-4 µg/dl, suggesting that inhibition of ALA-D may occur at

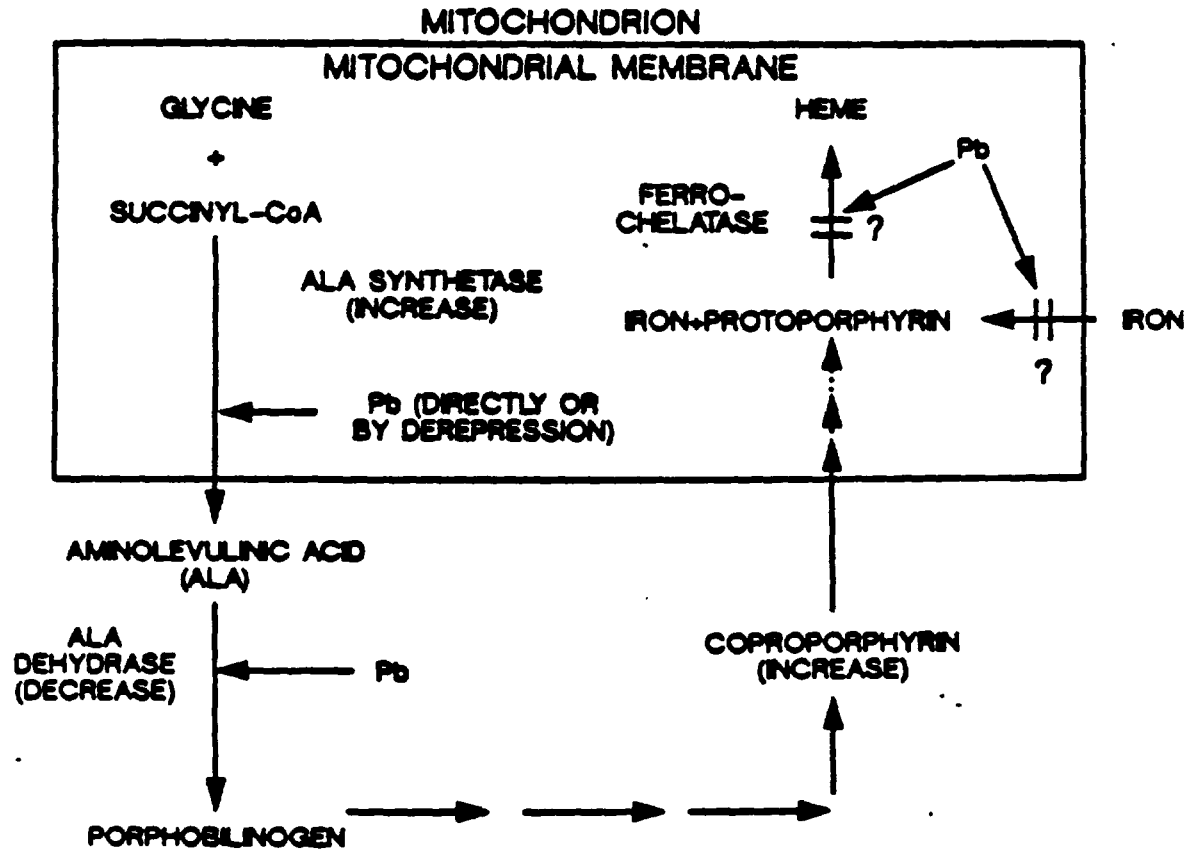


FIGURE 2-5

Effects of Lead on Heme Biosynthesis

Source: U.S. EPA, 1986b

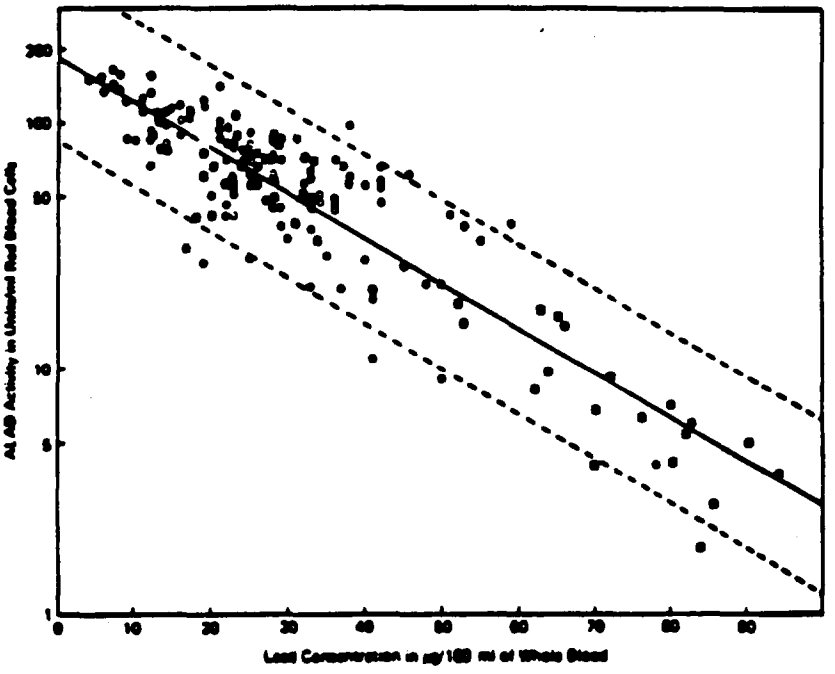


FIGURE 2-6

Blood ALA-D Activity As a Function of Blood Lead Level in 158 Adults. (Solid Circles, Medical Students; Open Circles, Workers in Print Shop; Solid Squares, Automobile Repair Workers; Open Squares, Lead Smelters and Shipscrapers)

Source: NAS, 1972

these low blood lead levels (Hernberg and Nikkanen, 1970; Hernberg et al., 1970; Roels et al., 1975, 1976; Lauwerys et al., 1978; Chisolm et al., 1985). The dose-response relationship for ALA-D inhibition at levels <20 µg/dℓ has not been completely characterized; therefore, the existence of a threshold has not been verified.

The extensive information regarding the effects of lead on EP levels in humans is critically reviewed in several Agency documents (U.S. EPA, 1986a; ATSDR/U.S. EPA, 1988). The threshold for elevated EP in children is ≈15 µg/dℓ (Roels et al., 1976; Piomelli et al., 1982; Hammond et al., 1985; Rabinowitz et al., 1986). A dose-response analysis based on the data from Piomelli et al. (1982) is shown in Figure 2-7. The dose-response relationships for elevated EP in children and adults when examined across a range of blood lead levels extending from 10-40 µg/dℓ indicate that children are more sensitive than adults and that adult females may be more sensitive than males (Roels et al., 1976). The lower range of blood lead levels at which EP levels become elevated is below that associated with decrement in blood hemoglobin levels and anemia (Hammond et al., 1985). Elevated protoporphyrin levels, although not necessarily an adverse effect per se, are indicative of disturbances in heme metabolism that may extend to other heme proteins.

The enzyme P5N is also inhibited by lead (Paglia and Valentine, 1975). This enzyme catalyzes the dephosphorylation of pyrimidine nucleotide monophosphates and plays an important role in the regulation of the levels of pyrimidine nucleotides within the erythroblast. The pathological significance of inhibition of P5N by lead is unknown; however, congenital deficiency of this enzyme, in which <10% of normal activity is present in the erythroblast, is associated with a syndrome of hemolytic anemia

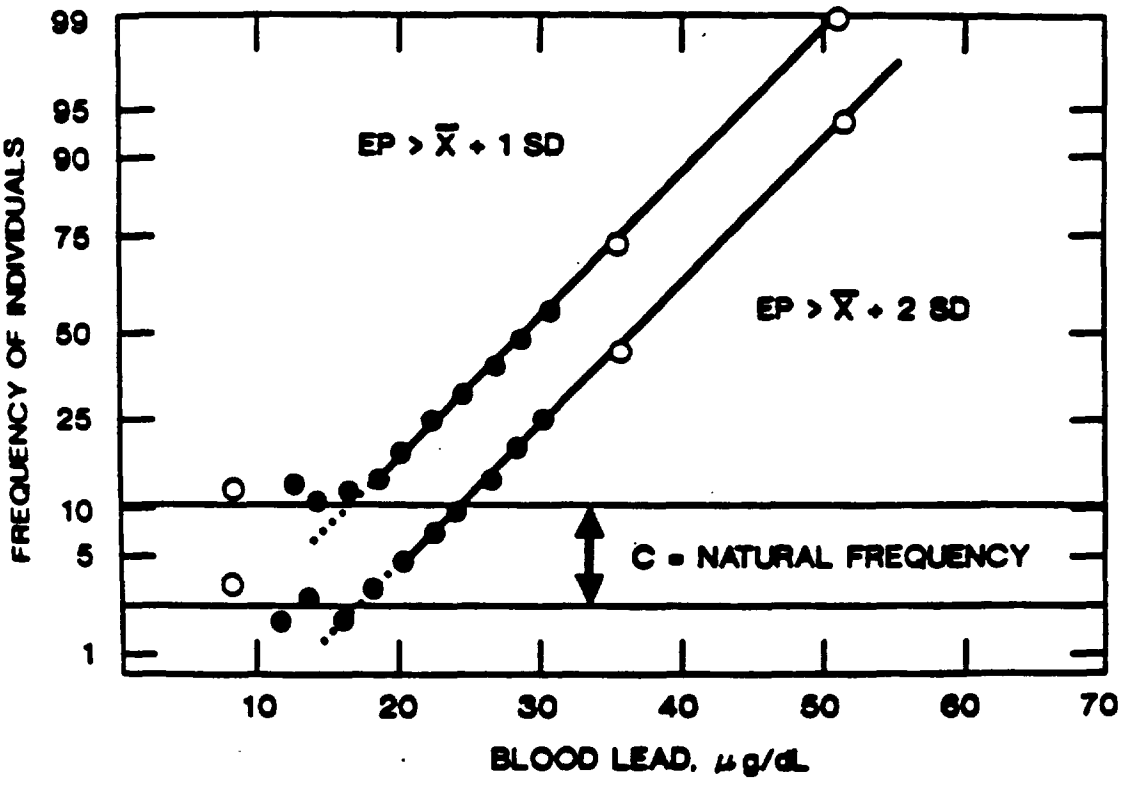


FIGURE 2-7

Probit Dose-Response Functions for Elevated Erythroblast Protoporphyrin as Function of Blood Lead Level in Children. (Geometric Mean ± 1 SD = 33 µg/dℓ; Geometric Mean ± 2 SD = 53 µg/dℓ)

Source: Piomelli et al., 1982

(Valentine et al., 1974). Thus, inhibition of erythroblast P5N may contribute to the anemia associated with relatively high blood lead levels (≥80 µg/dℓ) (Tola et al., 1973; Grandjean, 1979; Lilis et al., 1978; Wada et al., 1973; Baker et al., 1979). The inhibition of P5N may also contribute to a disruption of mRNA and protein biosynthesis in the erythroblast.

Inhibition of P5N in human erythrocytes can be detected from measurements of the levels of pyrimidine nucleotide monophosphate substrates for this enzyme or from measurements of catalytic activity of erythrocyte preparations. Levels of erythrocyte pyrimidine nucleotide monophosphate are elevated in children that have blood lead levels exceeding 30 µg/dℓ. This suggests that significant inhibition of P5N occurs at blood lead levels >30 µg/dℓ (Angle et al., 1982). Catalytic activity of erythrocyte P5N is inversely correlated with blood lead in children (Angle and McIntire, 1978; Angle et al., 1982). The correlation persists when examined across a range of blood lead levels extending from 7-80 µg/dℓ, suggesting that inhibition of P5N may occur at levels possibly <10 µg/dℓ (Figure 2-8).

In conclusion, the available information indicates the potential for undesirable effects on heme biosynthesis and erythroblast pyrimidine metabolism in children with blood lead levels >10-15 µg/dℓ, and possibly at lower levels.

2.3.3. Effects on the Kidney. Acute lead-induced nephrotoxicity is characterized by proximal tubular nephropathy. Characteristic lesions described in both humans and animals include nuclear inclusion bodies and mitochondrial changes in the epithelial cells of pars recta of the proximal tubule and impaired solute reabsorption (e.g., glucose, amino acids,

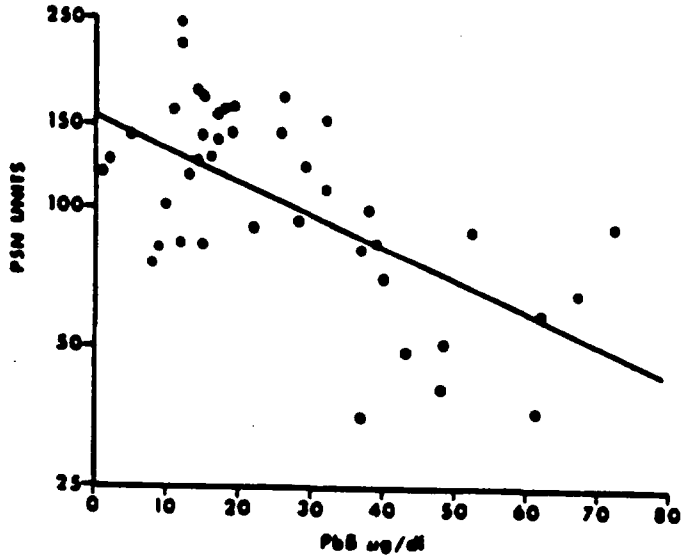


FIGURE 2-8

Erythrocyte Pyrimidine 5'-Nucleotidase Activity (P5N Units)
as a Function of Blood Lead Level in 25 Children, 1-5 Years Old

Source: Angle et al., 1982

phosphate). Chronic toxicity is characterized by interstitial fibrosis and decreased glomerular filtration rate (Goyer, 1982; U.S. EPA, 1986b; ATSDR/U.S. EPA, 1988).

Acute nephrotoxicity has been observed in children with lead encephalopathy and is associated with relatively high blood lead levels (i.e., >80 µg/dℓ) (Chisolm et al., 1955; Chisolm 1962, 1968; Pueschel et al., 1972; U.S. EPA, 1986b). Chronic nephropathy, indicated by nuclear inclusion bodies, mitochondrial changes, interstitial fibrosis and glomerular changes, has been associated with prolonged (≥10 years) occupational exposures and blood lead levels >40-60 µg/dℓ (Lilis et al., 1968; Cramer et al., 1974; Biagini et al., 1977; Weeden et al., 1975, 1979; Buchet et al., 1980; Hong et al., 1980).

2.3.4. Effects of Lead on Blood Pressure. The relationship between concurrent blood lead levels and blood pressure in adults has been examined in several epidemiological studies. Particularly notable are four large epidemiology studies: BRHS, NHANES II analysis and two studies conducted in Wales. The estimated change in mean systolic blood pressure for a doubling of blood lead, as assessed from analyses of these four large-scale studies (Pocock et al., 1988) is shown in Figure 2-9.

The BRHS study analyzed data on blood lead levels and blood pressure in 7735 middle-aged men (aged 40-49) from 24 British towns (Pocock et al., 1984, 1985, 1988). Systolic and diastolic blood pressure were positively correlated with blood lead levels across a range of blood lead levels extending from ≈10-40 µg/dℓ. Based on a linear regression analysis of the data, it was predicted that doubling of blood lead levels was associated with an increase of 1.45 mm Hg systolic pressure and 1.25 mm Hg diastolic pressure.

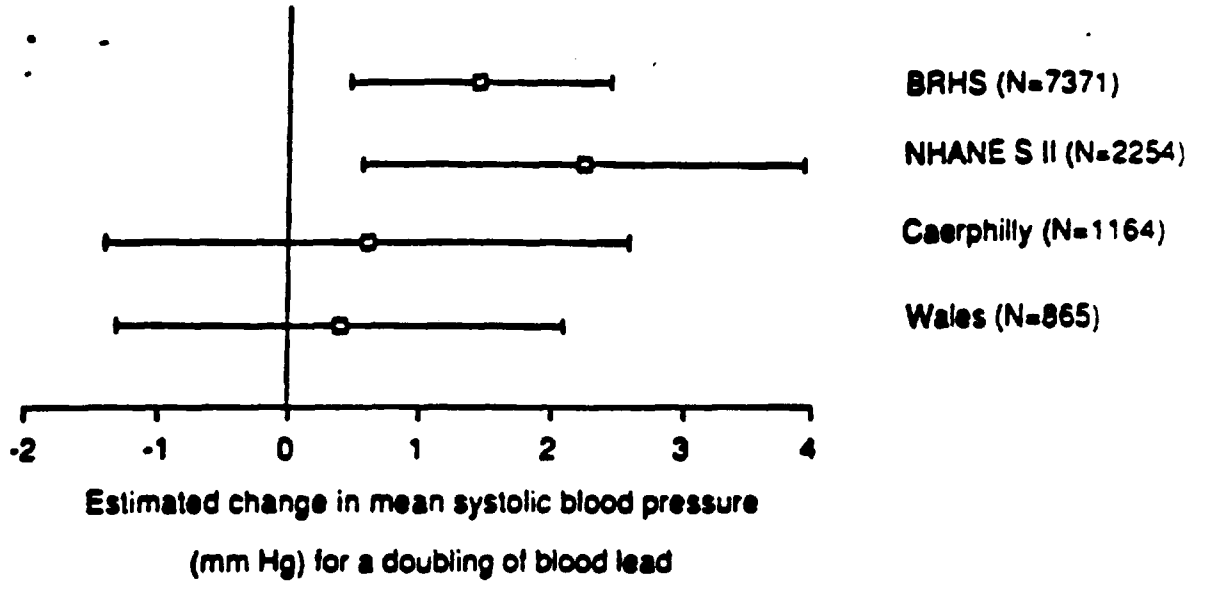


FIGURE 2-9

Comparison of Study Results from Four Larger-Scale Epidemiology Studies of Lead-Blood Pressure Relationships in Adult Men. BRHS, British Regional Heart Study (Pocock et al., 1988); NHANES II, National Health and Nutrition Evaluation Survey (Schwartz, 1988); Caerphilly and Wales, Welsh Studies (Elwood et al., 1988a,b). Shown are means and 95% confidence limits.

Source: Pocock et al., 1988

Several analyses of data on blood pressure and blood lead levels from NHANES II have been reported (Harlan et al., 1985; Pirkle et al., 1985; Landis and Flegal, 1987). Systolic and diastolic blood pressure was positively correlated with blood lead levels over a range of blood lead levels that extended from 7-34 μg/dℓ. Based on a linear regression analysis of data from ≈20,000 subjects, it was predicted that a doubling of blood lead levels (e.g., from 8-16 μg/dℓ) was associated with an increase of 2-3 mm Hg systolic blood pressure.

Two surveys conducted in Wales examined the relationship between blood lead and blood pressure (Elwood et al., 1988a,b). The Welsh Heart Programme analyzed data from 865 men and 856 women. Mean blood lead levels were 12 μg/dℓ for men and 10 μg/dℓ for women. A regression analysis was applied to the data. No statistically significant relationship between blood pressure and blood lead level was established. The Caerphilly Collaborative Heart disease study analyzed data from 865 adult males living in Caerphilly, Wales (Elwood et al., 1988b). Regression analysis did not reveal a statis- tically significant relationship between blood pressure and blood lead.

In addition to the four large-scale studies described above, preliminary analysis of a cross-sectional study from Canada was recently reported (Neri et al., 1988). This study analyzed data from 2193 subjects. A statistically significant relationship between blood lead levels and diastolic blood pressure was reported. Several small-scale studies have been reported that show significant relationships between occupational exposure to lead and blood pressure (Sharp et al., 1988; Weiss et al., 1988; Moreau et al., 1988).

Although the results of individual studies vary with respect to the quantitative relationship between blood lead and blood pressure, the weight of evidence provided by the several large scale epidemiology studies and

numerous small scale epidemiology studies supports the existence of a positive correlation between blood lead level and blood pressure. In addition, the results of numerous animal studies support a dose-response relationship between lead exposure and elevated blood pressure. Chronic exposure to inorganic lead increases blood pressure in laboratory animals (Victery, 1988), increases plasma renin activity (Vander, 1988) and appears to sensitize the vascular endothelium to pressor agents (Chai and Webb, 1988). The correlation between blood lead levels and blood pressure in humans appears to extend to blood lead levels <20 μg/dℓ, and possibly to as low as 7 μg/dℓ. This suggests that as blood lead level increases >7 μg/dℓ to levels ≥20 μg/dℓ, the risk for increased blood pressure increases. The precise function that describes the dose-effect relationship over a range of blood lead levels <40 μg/dℓ has not been characterized. This may reflect, in part, the relatively small quantitative effect of blood lead on blood pressure. Assuming a linear relationship between blood lead level and blood pressure, the BRHS and NHANES II analyses predict an increase of 1-3 mm Hg systolic blood pressure for a doubling of blood lead level (e.g., from 8-16 μg/dℓ). With such a low magnitude effect, detection of effects <10 μg/dℓ may not be possible even with large-scale epidemiology studies, such as the NHANES II analysis. Nevertheless, a sustained increase in blood pressure of only a few mm Hg may have a significant public health impact in terms of cardiovascular and related diseases (Pirkle et al., 1985).

2.3.5. Effects of Lead on Serum Vitamin D Levels. 1,25-Dihydroxycholecalciferol, the active from of vitamin D, is a hormone that plays an important role in the regulation of gastrointestinal absorption and renal excretion of calcium and phosphorus and in the mineralization of bone.

Deficiencies in 1,25-dihydroxycholecalciferol are associated with decreased bone mineralization and clinical syndrome of rickets in children. 1,25-Dihydroxycholecalciferol may also stimulate gastrointestinal absorption of lead (Smith et al., 1978). Serum levels of 1,25-dihydroxycholecalciferol are inversely correlated with blood lead in children (Rosen et al., 1980; Mahaffey et al., 1982). The correlation persists when examined across a range of blood lead levels extending from 12-60 µg/dℓ; however, the dose-effect relationship has not been characterized (Figure 2-10). Based on a linear regression analysis of data on serum 1,25-dihydroxycholecalciferol and blood lead levels in children as well as data on 1,25-dihydroxycholecalciferol levels in other vitamin D related clinical disorders in children, it has been predicted that increasing the blood lead levels from 12 µg/dℓ to 60 µg/dℓ will lower serum 1,25-dihydroxycholecalciferol to clinically adverse levels (Mahaffey et al., 1982). Chronic depression of serum 1,25-dihydroxycholecalciferol levels of a much smaller magnitude than that associated with frank clinical disorders of calcium and phosphate metabolism have the potential to alter bone development and growth in children; therefore, blood lead levels >12 µg/dℓ should be considered potentially undesirable with respect to changes in 1,25-dihydroxycholecalciferol levels in children.

2.4. DEVELOPMENTAL/REPRODUCTIVE TOXICITY AND GENOTOXICITY

2.4.1. Mental Development in Infants and Children. The effects of prenatal and neonatal lead exposure on fetal and neonatal mental development have been examined in several epidemiological studies. Four prospective studies initiated in the cities of Boston, Cincinnati, Cleveland and Port Pirie, Australia are particularly notable. Based on an extensive

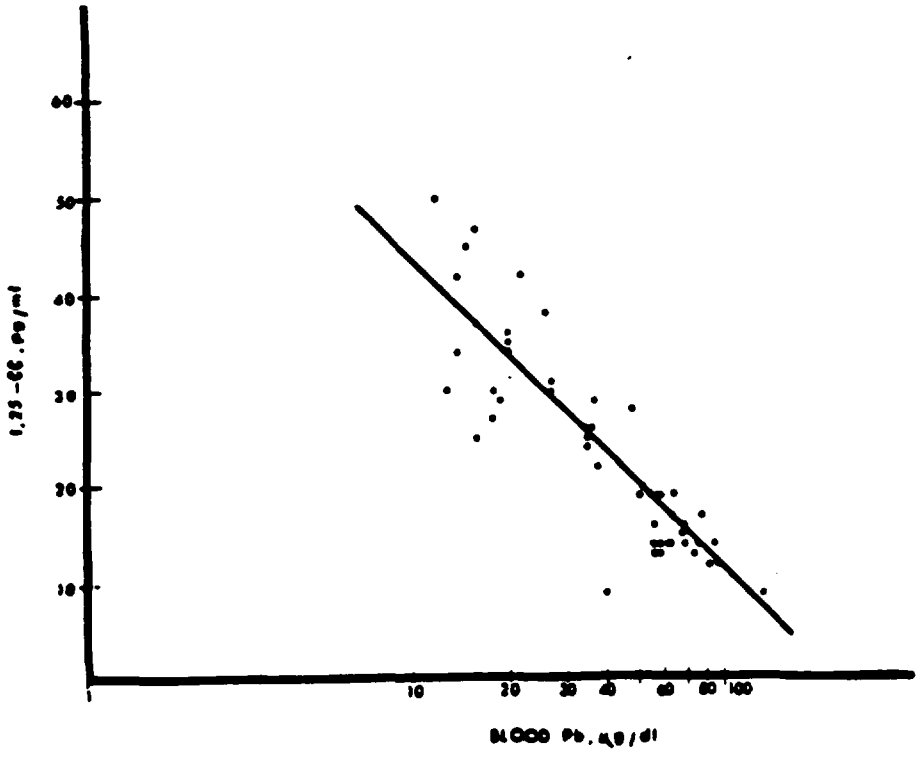


FIGURE 2-10

Serum 1,25-Dihydroxycholecalciferol Levels as a Function of Blood Lead Levels in 50 Children, 2-3 Years Old

Source: Mahaffey et al., 1982

evaluation of these studies, the EPA concluded that "All of these studies taken together suggest that neurobehavioral deficits, including declines in Bayley MDI scores and other assessments of neurobehavioral function, are associated with prenatal blood lead exposure levels on the order of 10-15 µg/dℓ, and possibly even lower, as indexed by maternal or cord blood lead concentrations" (U.S. EPA, 1986b). Evaluations of more recent follow-ups reinforce this conclusion.

Boston prospective study. The Boston study consisted of a longitudinal analysis of mental development in infants (Bellinger et al., 1987a,b, 1989a). Infants were classified according to "low," "mid" or "high" exposure groups, based on cord blood lead levels at birth: "low," <3 µg/dℓ; "mid," 6-7 µg/dℓ; "high," 10-25 µg/dℓ. The Bayley MDI was administered to each child at ages 6, 12, 18 and 24 months. Data were collected on a large number of social and medical covariates, including care taking and parental intelligence. A deficit of 4.8 points on the MDI was detected in children whose blood lead levels were 10-25 µg/dℓ at birth, as compared with children whose blood lead levels were <3 µg/dℓ at birth (Bellinger et al., 1987a). A plot of covariated-adjusted MDI scores vs. age at testing for each group in the Bellinger et al. (1987a) study is shown in Figure 2-11.

Preliminary results of an analysis of data collected in a follow-up study has been reported (Bellinger et al., 1987b, 1989b). At age 57 months, scores on the McCarthy Scales GCI were inversely associated with blood lead level at age 24 months (3-25 µg/dℓ), but were not correlated with cord blood lead levels at birth. Improvement of cognitive performance, as assessed from the GCI, appeared to be related to concurrent blood lead as well as prenatal blood lead and socioeconomic factors. It appeared to be

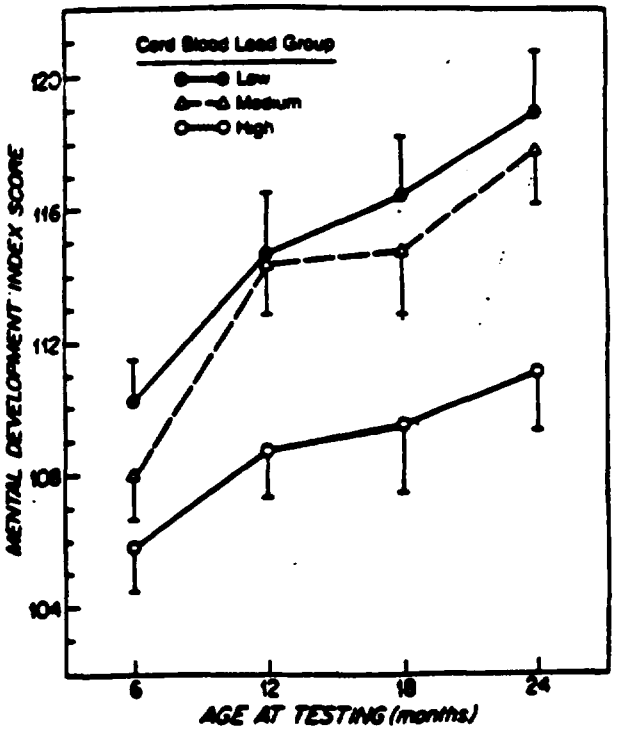


FIGURE 2-11

Mental Development Index Score (Covariate adjusted, Mean and SD) as a Function of Age for Children Grouped into Three Ranges of Cord Blood Lead level; Low, <3 µg/dℓ; Medium, 6-7 µg/dℓ; High, 10-25 µg/dℓ

Source: Bellinger et al., 1987a

more likely that cognitive deficits persisted to age 57 months in children with higher postnatal blood lead levels or less favorable socioeconomic factors or both.

The data reported thus far from the Boston study indicate that lead levels within or exceeding the range 10-25 μg/dℓ are associated with decrements or delays in mental development. This is consistent with a 10-15 μg/dℓ range of concern for undesirable effects in children.

Cincinnati prospective study. The study initiated in Cincinnati consisted of a longitudinal analysis of mental and physical development in infants (Dietrich et al., 1987, 1988). MDI was measured at 3, 6, 12 and 24 months. Structural equation modeling, a form of regression analysis, was used to examine statistical interactions between MDI scores and both prenatal blood lead levels (range 1-27 μg/dℓ), cord blood lead levels (1-28 μg/dℓ) and neonatal (10-day) blood levels (1-22 μg/dℓ), as well as several other possible covariables, including medical and socioeconomic parameters. The analysis revealed a statistically significant relationship between elevated prenatal and cord blood lead and lower MDI scores at 3 or 6 months of age. At 12 months of age, however, neither prenatal nor cord blood levels were significantly related to MDI scores although the relationship between neonatal (10-day) blood lead and MDI scores remained statistically significant. At 24 months, neither prenatal, cord blood nor neonatal (10-day) blood lead levels were significantly related to MDI scores. Thus, the effects on mental development detected in the Cincinnati study appeared to be transient. The investigators hypothesized that the transiency of the decrements in MDI scores might reflect a "catch up" response of infants related to lower birth weights or gestational age in the infants with higher prenatal blood lead levels (Section 2.4.2.).

Postural sway was measured in a small group of 6-year-old children from the Cincinnati cohort (Bhattacharya et al., 1988). Peak blood level at 2 years (9-50 µg/dℓ) was significantly related to postural sway at 6 years. This suggests the possibility of persistent deficits in balance related to childhood lead exposure.

The subjects in the Cincinnati study were not grouped by blood lead as in the Boston study; therefore, it is more difficult to categorize effects associated with a specific range of blood lead levels between 1 and 28 µg/dℓ. Nevertheless, the study corroborates some of the important findings of the Boston study because both studies detected an apparent effect of lead on mental development (MDI scores) during the first 12 months in infants exposed to prenatal blood lead levels or neonatal blood lead levels <25 µg/dℓ. Thus, the study supports 10-15 µg/dℓ as a range of concern for undesirable effects in children.

Cleveland prospective study. The longitudinal study initiated in Cleveland is unique because it examined a series of neurobehavioral measures of neonatal sensorimotor function. The tests included the Brazelton NBAS for Habituation, Orientation, Motor Performance, Range of State, Autonomic Regulation and Abnormal Reflexes, and the G-R for General Maturation, Soft Signs and Muscle Tonus (Ernhart et al., 1986). The results of a multiple regression analysis indicated that decreased scores for G-R Soft Signs and NBAS were significantly related to cord lead levels (2-15 µg/dℓ) but not maternal blood lead (3-12 µg/dℓ). The results of follow-up studies at 6, 12, 24 and 36 months were somewhat equivocal with respect to the effects of lead on mental development (Ernhart et al., 1987). Lower scores on the PDI and MDI of the Bayley Scales, and the KID at 6 months were significantly

related to higher maternal blood lead (3-12 µg/dℓ) but not to cord blood lead (3-15 µg/dℓ). Concurrent 6-month blood lead was positively associated with KID score (e.g., higher blood lead levels were associated with higher KID scores). A portion of the Cleveland cohort was tested at 4 years, 10 months on the WPPSI. After accounting for covariates, significant effects of lead were not detected (Ernhart and Morrow-Tlucak, 1987).

The Cleveland study examined a cohort having a range of relatively low blood lead levels (<15 µg/dℓ). This may explain why relatively few of the infant development indices were found to be related to blood lead, even though some of the tests were redundant. It is likely that >50% of women in this cohort consumed considerable amounts of alcohol during their pregnancy. It is possible that the alcohol-induced effects on physical and mental development of newborns mask any subtle effects of lead. Nevertheless, the study corroborates the major finding of the Boston and Cincinnati studies; the existence of a positive relationship between MDI scores during the first year of postnatal life and blood lead levels.

Port Pirie prospective study. The Port Pirie study examined cohorts of infants born to mothers living in the vicinity of a lead smelting operation in Port Pirie, Australia, and infants from outside the Port Pirie area. Maternal blood and cord lead levels were slightly but significantly higher in the Port Pirie cohort than in the cohort from outside Port Pirie; mean cord blood lead was 10 vs. 6 µg/dℓ. Reduced MDI scores were significantly associated with higher integrated postnatal blood lead levels and with 6-month blood lead levels, but not with prenatal or delivery blood lead levels. Mean blood lead levels in the children were 14 µg/dℓ at 6 months of age and 21 µg/dℓ at 15 and 24 months of age (McMichael et al., 1986; Vimpani et al., 1985; Baghurst et al., 1987). The results of a linear

regression analysis of the data indicated an apparent 4-point deficit in MDI for every 10 µg/dℓ increase in blood lead. After making adjustments for maternal IQ and care-taking environment, this deficit decreased to 2 points for every 10 µg/dℓ increase in blood lead. Follow-up study of these children at 4 years of age included the McCarthy Scales of Children's Abilities. Deficits in GCI scores were associated with increased integrated postnatal blood lead levels (McMichael et al., 1988). Linear regression analysis of data on blood lead and GCI scores indicated that an increase in integrated postnatal blood lead level from 10-30 µg/dℓ was associated with a 7-point decrease in GCI score.

Mexico City prospective study. Preliminary results of a pilot study in Mexico City for a longitudinal investigation of developmental outcomes related to lead esposure and other factors have been reported by Rothenberg et al. (1989). Approximately 50 mothers were sampled for blood lead levels at 36 weeks (M36) of pregnancy and delivery (MD); umbilical cord blood lead (UC) was also sampled at delivery. Mean maternal blood lead levels were 15.0 µg/dℓ at 36 weeks of pregnancy and 15.4 µg/dℓ at delivery. Mean cord-blood lead levels at delivery were 13.8 µg/dℓ. The Brazelton NBAS was administered to the infants at 48 hours and 15 and 30 days after birth.

The data were analyzed by calculating the trend of the NBAS subscale scores over the first 30 days by linear regression analysis and by computing the difference in M36 and MD values or M36 and UC values. The relationships among the various primary and secondary measures were then examined through bivariate correlations and multivariate repression analyses. Significant bivariate correlations were found between UC blood lead and the 30-day trend in NBAS Abnormal Reflexes ($r=0.299$, $p<0.05$), between the M36-MD blood lead

difference and Regulation of States (r=0.378, P<0.05), and between the MD-UC blood lead difference and Abnormal Reflexes (r= -0.451, p<0.01). The signs of all the correlations reflected impairment of functions. Stepwise multiple regression modeling with all covariates entered before the lead variable revealed that the blood lead differentials for M36-MD and for MD-UC accounted for a significant amount of the variance in the Abnormal Reflexes trend (p=0.03 for each). Similarly, M36-MD accounted for a significant amount of the variance (p=0.025). However, UC alone was no longer significantly associated with Abnormal Reflexes.

Rothenberg et al. (1989) also evaluated physical development outcomes at birth in their cohort. After controlling for covariates, multiple regression analyses indicated that M36-MD and M36-UC each accounted for a significant amount of the variance in birthweight (p<0.05), M36-UC accounted for a significant amount of the variance in chest circumference (p=0.054), and UC and M36-UC accounted for a significant amount of the variance in trunk length (p=0.06).

The results of the most recent studies of lead and mental development are summarized in Figure 2-12. The above four prospective studies differed greatly in design and scope, and discrepancies in the results are to be anticipated given the complex nature of the endpoints evaluated. Nevertheless, when taken together with the results of cross-sectional studies (Hawk et al., 1986; Ferguson et al., 1988a,b,c; Hatzakis et al., 1987; Lyngbye et al., 1989; Fulton et al., 1987), corroborative evidence for effects on physical and mental development in infants and children exposed to lead is provided. All four studies detected a relationship between elevated blood lead levels and lower mental development (MDI scores) during the first 12 months in infants exposed to prenatal or postnatal (or both)

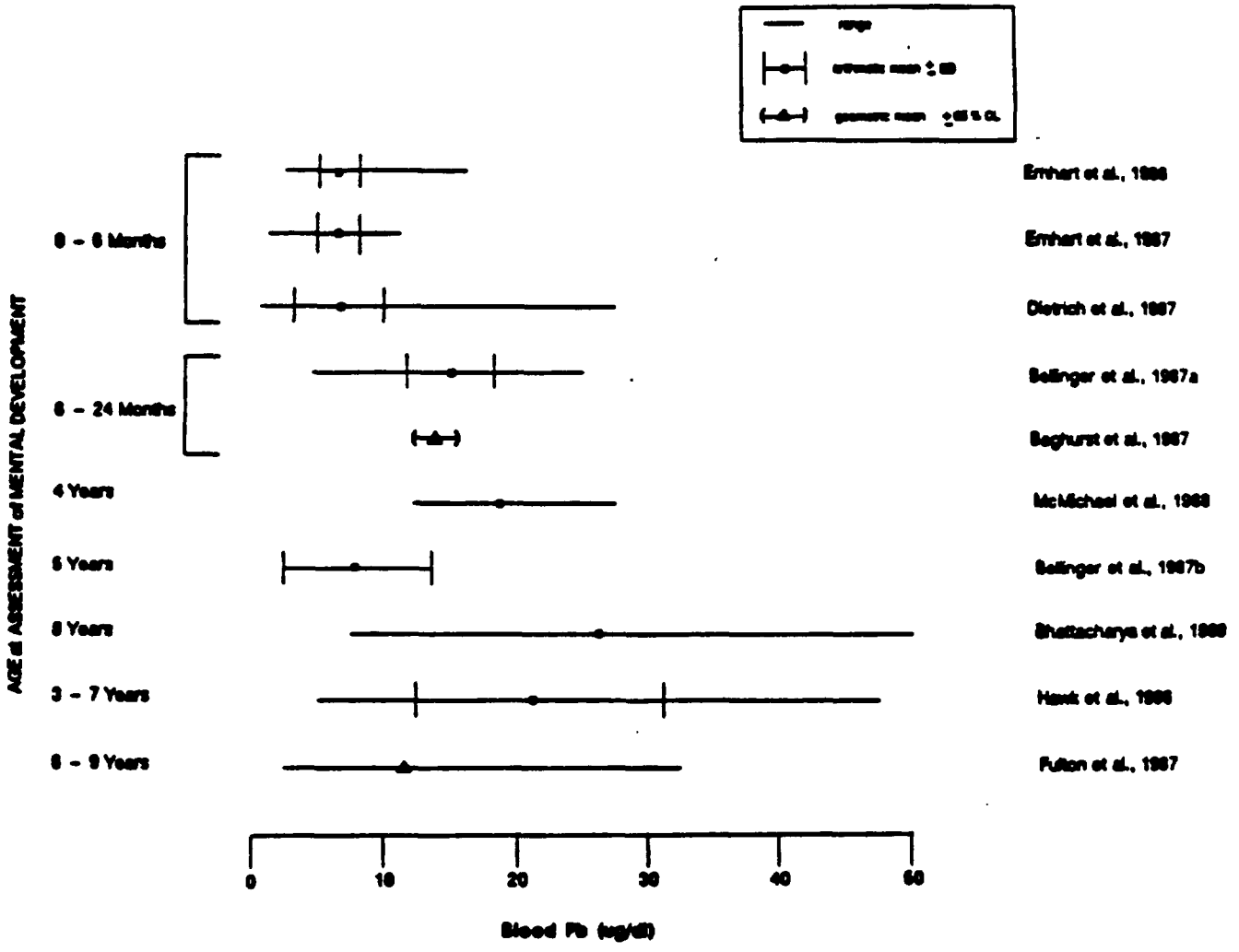


FIGURE 2-12

Comparison of Results from Prospective and Cross-Sectional Studies of Mental Development. [Shown is the range of blood lead levels (solid line) for which significant statistical associations for various indices of mental development and blood lead level were detected. Studies are organized vertically according to the age at which the deficit or delay was observed.]

blood lead levels <30 µg/dℓ. Thus, it is probable that as blood lead levels approach >30 µg/dℓ, the risks for undesirable effects increase. It is more difficult to draw conclusions regarding the exact dose-effect relationship over the range of blood lead levels extending <30 µg/dℓ. The Boston study (Bellinger et al., 1987a) indicates significant effects on mental development related to blood lead levels within the range 10-25 µg/dℓ. The Cincinnati (Dietrich et al., 1987), Cleveland (Ernhart et al., 1986, 1987) and Port Pirie (Baghurst et al., 1987; McMichael et al., 1988) studies indicate effects within the ranges of 1-28, 3-15 and 8-32 µg/dℓ, respectively. Given the results of the these studies, it is reasonable to conclude that any threshold that might exist is in the range of 10-15 µg/dℓ blood lead, and possibly lower.

2.4.2. Growth Deficits. The structural analysis used in the Cincinnati prospective study indicated the possibility that the decrement in MDI scores might have been secondary to lead-related effects on either gestational age at birth or fetal birth weight (Dietrich et al., 1987). A separate regression analysis of the Cincinnati data examined the relationship between prenatal blood lead levels (1-26 µg/dℓ) and birth weight (Bornscheim et al., 1989). Decreased birth weight was related to increased maternal blood lead levels. Maternal age was identified as a major covariate; thus, it appeared as if a given blood lead level was associated with a larger decrement in birth weight in older women (e.g., 30 years) than in younger women (e.g., 18 years). In a subsequent analysis of the Cincinnati data, growth rate (height) in infants, 3-15 months of age, was inversely correlated to postnatal blood lead increases. Mean blood lead levels increased from 5.3 µg/dℓ at 3 months to 14.6 µg/dℓ at 15 months (Shukla et al., 1987).

Effects of lead on pre- and postnatal growth are supported by several other studies including Schwartz et al. (1986), Ward et al. (1987), Fahim et al. (1976) and Huel and Boudeve (1981).

2.4.3. Effects on Fertility and Pregnancy Outcome. Severe occupational exposure to lead has been associated with increased incidence of spontaneous abortion (U.S. EPA, 1986b). However, early studies do not provide reliable descriptions of dose-effect relationships. The Port Pirie cohort study described in Section 2.4.1. examined pregnancy outcome in populations living near and distant from a lead smelter. The risk for pre-term delivery was positively related to maternal blood lead, over a range of 8-32 µg/dℓ (McMichael et al., 1986). The relative risk for pre-term delivery was 4.4 for maternal lead levels >14 µg/dℓ (range 14-32 µg/dℓ, mean 17 µg/dℓ).

Depressed sperm production and development has been associated with occupational exposure to lead. Based on studies by Lancranjan et al. (1975) and Wildt et al. (1983), the Agency concluded that undesirable effects on sperm or testes may occur in men as a result of chronic exposures leading to blood lead levels of 40-50 µg/dℓ (U.S. EPA, 1986b).

2.4.4. Genotoxicity. Studies relating to genotoxicity of lead are reviewed in the Air Quality Criteria Document for Lead (U.S. EPA, 1986b). Structural chromosomal aberrations and increased sister chromatid exchanges in peripheral lymphocytes have been associated with chronic exposure to lead resulting in blood lead levels in the range of 24-89 µg/dℓ, although effects were not observed over this range of blood levels in numerous studies (U.S. EPA, 1986b). This may reflect the differences in exposure duration in relation to lymphocyte proliferation and turnover. In one study, increased sister chromatid exchange was positively correlated with

exposure duration and zinc protoporphyrin levels, but correlated poorly with blood lead level (Grandjean et al., 1983).

Bacterial systems generally are regarded as inappropriate for assaying metal ions. The U.S. EPA (1989b) reviewed the data on chromosome aberrations in higher organisms; alterations in chromosome structure appeared to depend on factors such as harvest time following exposure, duration and route of exposure, and test system. Furthermore, diet influenced the chromosome breakage induced by lead in vivo. Lead-exposed animals on calcium-deficient diets have exhibited a higher incidence of chromosomal aberrations than lead-exposed animals on standard diets. Other studies reviewed by the U.S. EPA (1989b) demonstrated that lead compounds induce cell transformation in Balb/3T3 mouse cells and Fisher 344 rat embryo cells infected with the Rauscher murine leukemia virus. Collectively, these studies suggest that lead produces undesirable effects on chromosomes.

2.5. SUMMARY

Correlation and regression analyses of data on blood lead levels and various health effects point to a spectrum of undesirable effects that become apparent in populations having a range of blood lead levels extending upward from 10-15 µg/dℓ. These include effects on heme metabolism and erythrocyte pyrimidine nucleotide metabolism, serum vitamin D levels, mental and physical development of infants and children and blood pressure in adults. Although correlations between blood lead levels and certain effects persist when examined across a range of blood lead levels extending <10 µg/dℓ, the risks associated with blood lead levels <10 µg/dℓ are less certain. Although it is not possible to define with certainty the risks associated with any given lead-related effect (e.g., neurobehavioral deficits and increased blood pressure), the weight of evidence suggests that

blood levels in the range of 10-15 μg/dℓ or possibly lower are likely to be associated with one or more undesirable effects. Therefore, regulatory decisions regarding environmental lead should take into account the evidence for potentially adverse health effects at relatively low blood lead levels.

The results of studies on the effects of lead in children are summarized in Figure 2-13. Evidence from several studies supports a relationship between prenatal and postnatal lead exposure in infants and young children, as indexed by blood lead levels, and a variety of diverse effects. These include impaired or delayed mental and physical development, decreased heme biosynthesis and other biochemical effects on erythrocytes, and decreased levels of serum vitamin D levels. Although a threshold for these effects has not been established, the evidence suggests that it may lie within 10-15 μg/dℓ or possibly lower. As blood lead levels increase above the range of 10-15 μg/dℓ, the risk for more pronounced effects on all of the above endpoints increases. At levels >30 μg/dℓ, the risk for nephrotoxicity and overt neurological effects (e.g., encephalopathy) becomes substantial. Thus, infants and children appear to be at least as sensitive to lead than adults if the dose-effect relationship for these effects in children is compared with that for effects on blood pressure in adults.

Effects of lead on development are particularly disturbing in that the consequences of early delays or deficits in physical or mental development may have long-term consequences over the lifetime of affected individuals. Furthermore, mouthing behavior is a significant mechanism for lead uptake in infants. Thus, infants and young children can be expected to be particularly susceptible to changes in lead levels in dust and dirt (see Chapter 4

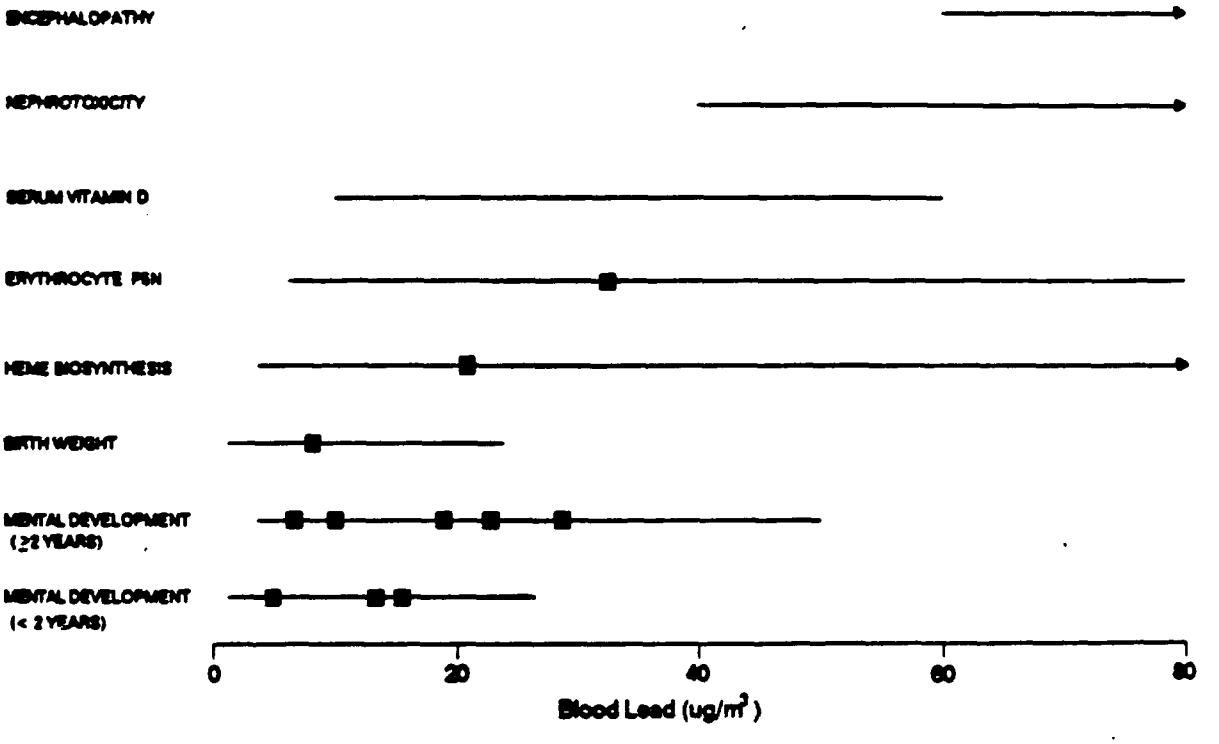


FIGURE 2-13

Summary of Studies Relating Blood Lead Levels and Effects on Various Toxicity Endpoints in Infants and Children. Lines represent range of blood leads for which significant statistical associations were detected for each effect. Solid squares indicate mean blood levels for the population studied.

for further discussion). For these reasons, infants and children (up to 2 years) can be considered to be the critical sensitive population on which to focus regulatory decisions regarding environmental lead.

Currently available information on the biokinetics of inorganic lead indicate that oral exposure to lead in food and beverages and nonfood sources such as dust and soil will be the most quantitatively significant route of uptake of environmental lead in most populations of infants and children. Therefore, abatement strategies that focus on these sources are likely to be the most productive for lowering blood lead levels.

Numerous epidemiological studies have indicated the importance of fetal lead exposure on lead burdens in infants and children. These studies (Cincinnati and Port Pirie) also indicate that children born with high lead body burdens may be more vulnerable to further exposure in early childhood. This further emphasizes the importance of focusing regulatory policies on children, who ultimately pass their lead burdens on to future generations.

Although the health effects of lead have been correlated with levels of lead in blood, the largest physiological compartment for lead distribution is bone, which has a relatively long elimination half-life. Lead is slowly released from bone and will distribute to other tissues when uptake levels are decreased. As a result, new steady-state levels of lead in blood may be achieved years after uptake levels decrease. Release of lead from bone may be accelerated in conditions of metabolic stress, including pregnancy, in which resorption of bone occurs. The relatively slow turnover of bone lead must be considered when evaluating the potential health impact of decreasing levels of lead in important exposure media. Physiologically-based pharmacokinetic models that incorporate age-related changes in bone metabolism and other physiological parameters that affect the distribution and excretion of lead can be particularly useful for predicting the impact of regulatory or abatement decisions on blood lead levels.

3. EXPOSURE ASSESSMENT

3.1. BIOLOGICAL EFFECTS: ENVIRONMENTAL EXPOSURE

The emerging evidence of a constellation of biochemical effects, along with subtle health effects at low levels of lead exposure (≤30 µg/dℓ), is considered indicative that low-level lead exposure has a far-reaching impact on fundamental cellular enzymatic, energy transfer and calcium homeostatic mechanisms. These effects can be expressed in infants and children as deficits in neurobehavioral and physical developments, and in adults as elevations in blood pressure. With higher levels of exposure (blood lead levels >30 µg/dℓ), overt symptoms of lead toxicity appear in the form of anemia, neurological impairment (e.g., encephalopathy), reproductive abnormalities and nephropathy.

The highest risks for adverse health effects from exposure to environmental lead in most populations are likely to be associated with infants and young children. Hence, risk assessment efforts related to environmental lead usually focus on this segment of the population. The exceptional vulnerability of infants and young children reflects an apparently innate sensitivity of developing organisms to lead, as well as a variety of physiologic and behavioral factors that facilitate their exposure to relevant environmental media. It is important to emphasize that exposure to humans begins in utero with the transplacental transfer of lead from mother to fetus. Thus, infants are born with an initial lead burden that reflects prior environmental exposure of the mother and, to some extent, in utero exposure of the mother. Environmental exposure that begins with birth adds to this preexisting burden and may be transferred to the next generation of infants.

Environmental exposure during the earliest period of infancy (0-6 months) is derived largely from the diet and, to a lesser extent, inhalation of indoor airborne lead. With the onset of floor activity and crawling, oral intake from indoor and outdoor dust and soil begins to contribute significantly and eventually becomes the single largest source of lead uptake. An estimated 70% of total lead uptake in 2-year-old children living near a lead point source (e.g., smoke stacks, smelter) is derived from ingestion of dust and soil (U.S. EPA, 1989a). The importance of dust and soil reflects the behavioral tendencies of infants and young children to crawl and play on floors and soil surfaces and to engage in extensive hand-to-mouth activity. The latter consists of thumb and finger-sucking and placing objects from the environment into their mouths. Pica, or excessive and intentional ingestion of nonfood items including soil, plaster and wood, occurs in some infants and young children and can contribute substantially to oral intake of lead (Binder et al., 1986; Clausing et al., 1987; Calabrese et al., 1989). Paint and plaster pica can be an extremely important exposure mechanism for infants and young children living or playing in or around structures containing deteriorating leaded paint or plaster.

In addition to behavioral characteristics that facilitate lead exposure, nutritional factors may also contribute to the vulnerability of infants and young children to lead. The nutritional requirements for rapid physical growth during the first 3 years render this age group susceptible to a variety of nutritional deficits, including iron, copper and zinc deficiencies. As discussed in Section 2.2.1.2., deficiencies of these minerals are associated with increased gastrointestinal absorption of lead in animals.

In general, inhalation is a quantitatively minor route of exposure for infants and children. Nevertheless, children may be more vulnerable than adults to exposure to airborne lead particles. Physiologic characteristics of the respiratory tract of infants and children result in higher deposition efficiencies of inhaled airborne particles than in adults (Phalen et al., 1985; Xu and Yu, 1986).

To fully appreciate the significance of childhood lead exposure as a critical focus of risk assessment methodology, the above considerations must be placed in perspective with serious potential for long-term consequences of neurobehavioral and developmental effects encountered at an early age. This does not trivialize the importance of long-term exposure and effects of lead in adults. The relationships reported to exist between systemic arterial blood pressure and concurrent blood lead level in adults suggest that low-level environmental exposure may have important health consequences for adults. It remains to be seen, however, whether such effects are related to chronic exposure extending from childhood or infancy to the adult. The importance of prospective epidemiological study designs in this area cannot be overemphasized. Regardless of the outcome of such studies, the long biological half-life of lead in bone and the potential for transplacental transfer of lead translates into additional risk factors for the fetus and for the infants of mothers exposed during childhood.

3.2. MULTIMEDIA LEAD EXPOSURES: AIR, SOIL, DUST, WATER, PAINT

Humans are typically exposed to lead in a variety of media as a result of the transfer of airborne lead to soil, water and food (Figure 3-1). The primary anthropogenic inputs to the air are automobile exhaust and industrial emissions. Natural inputs to the air can include geological

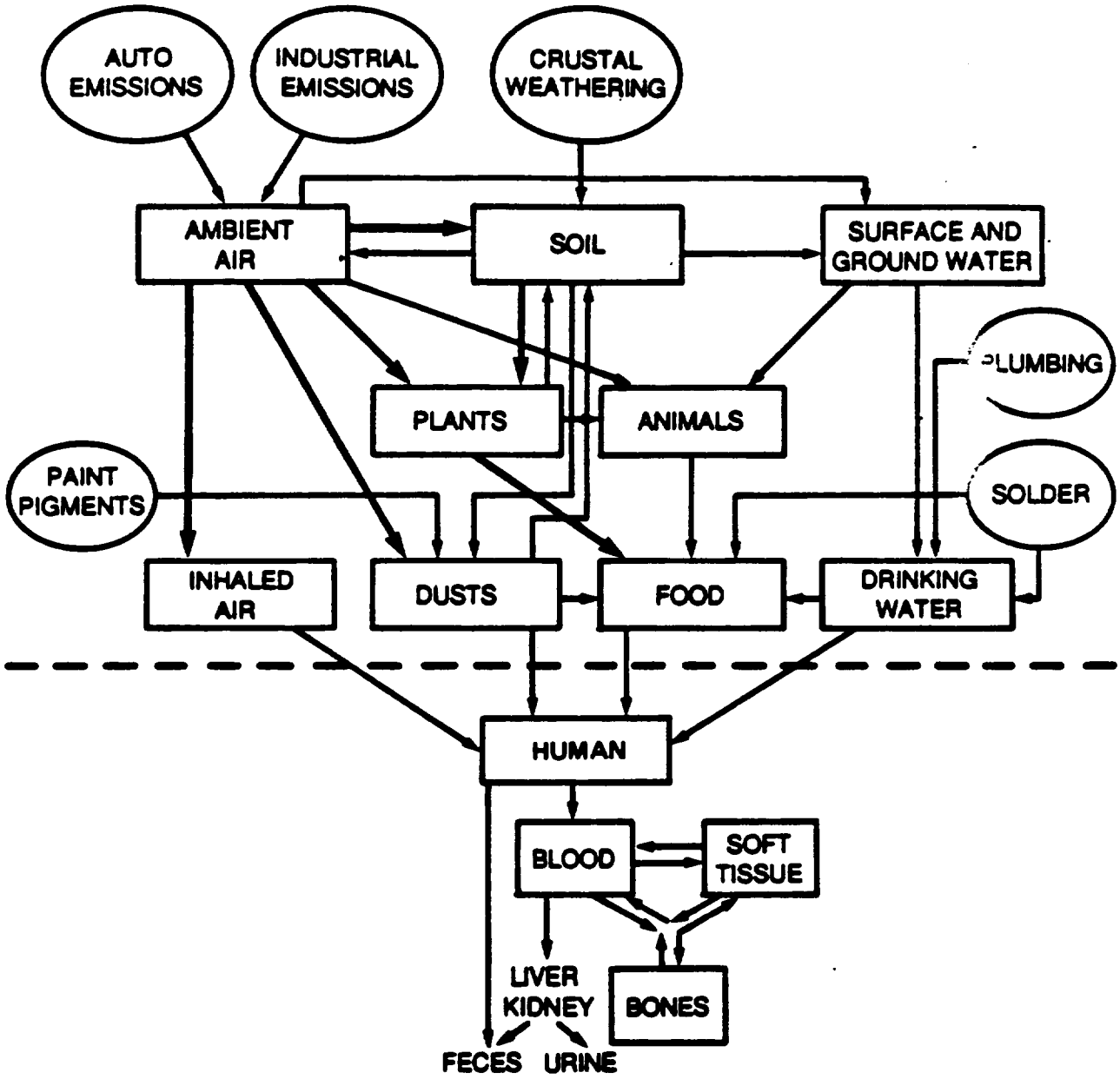


FIGURE 3-1

Pathways of Lead from the Environment to Humans

Source: U.S. EPA, 1986b

processes such as volcanic activity and crustal weathering. Emissions to ambient air eventually deposit in soil and ambient water, creating secondary exposure sources that include dust, soil, food and water. Additional inputs to water and food include lead pipes and solder joints in drinking water delivery systems and in food containers. Lead-based paint can also be an important source of contamination of house and street dust. Other potential sources of lead exposure include cosmetics (surma) and folk medicines (Healy et al., 1982). Shown in Table 3-1 are typical levels of lead in various media, including ambient air, in the United States (U.S. EPA, 1989a).

Although air emissions and lead paint are the primary anthropogenic sources of environmental lead, oral intake, rather than inhalation, is generally the predominant route of intake for humans. Intake occurs through ingestion of food and beverages, and in infants and children, through ingestion of dust and soil.

3.2.1. Lead in Air. Whereas, at one time, automobile exhaust accounted for ≈90% of all air emissions in the United States, the recent phase-down of lead content of gasoline and reductions in usage of leaded gasoline have and will continue to substantially decrease the contribution of automobile exhaust to air lead (U.S. EPA, 1986b). Lead in automobile exhaust originates from the combustion of gasoline containing organic lead additives, primarily tetraethyl and tetramethyl lead. Lead is emitted from vehicles primarily as particles of inorganic lead, with a small percentage as volatile lead alkyls. Of the automotive lead emissions deposited, ≈50% is within less than a few kilometers of roadways, whereas smaller particles can travel for thousands of kilometers (Huntzicker et al., 1975; U.S. EPA, 1986b).

TABLE 3-1

Typical Lead Concentrations in Various Exposure Media[a]

Medium	Rural Area	Urban Area	Near Point Source(s)[b]	Reference
Ambient air (μg/m3)[c]	0.1	0.1-0.3	0.3-3.0	U.S. EPA, 1989a
Indoor air (μg/m3)	0.03-0.08	0.03-0.2	0.2-2.4	U.S. EPA, 1986b
Soil (ppm)	5-30	30-4500	150-15,000	U.S. EPA, 1986b; Mielke et al., 1983
Street dust (ppm)[e]	80-130 (90)	100-5000 (1500)	(25,000)	Nriagu, 1978; U.S. EPA, 1986b
House dust (ppm)[e]	50-500 (300)	50-3000 (1000)	100-20,000 (10,000)	U.S. EPA, 1989a; Landrigan et al., 1975; Morse et al.,1979; Angle and McIntire, 1979
Typical Foods (ppm)	0.002-0.8	0.002-0.8	0.002-0.8	Flegel et al., 1988
Water (μg/ℓ)	5-2100	5-2100	5-2100	U.S. EPA, 1989a; Gardels and Sorg, 1989
Paint[f] (mg/cm2)	<1 to >5	<1 to >5	<1 to >5	U.S. EPA, 1989a

[a]Source: U.S. EPA, 1989a

[b]Within 2-5 km of sources including primary and secondary lead smelters, battery plants

[c]Represents quarterly averages monitored in 1986

[d]Range of indoor/outdoor ratios used (0.3-0.8) from U.S. EPA (1986b) except near point sources where large particles predominate and infiltration into homes is low; ratio appears to be closer to 0.3 (Cohen and Cohen, 1980).

[e]Values in parentheses represent estimates provided in U.S. EPA (1986b) as typical averages.

[f]Since there may be several layers of lead-based paint on a given surface, absolute concentration of lead is less useful than mg/cm2. Surveys by HUD in Pittsburgh showed that >70% of pre-1940 dwelling units and 20% of post-1960 units had at least one surface with >1.5 mg/cm2 lead paint (NAS, 1988).

Sources of industrial emissions include fugitive emissions from lead mining, primary and secondary lead smelting, battery plants, and combustion of oil, coal and municipal waste (U.S. EPA, 1986b). Dispersal of particles released from such processes depends on meteorological variables, including wind speed and direction and precipitation. The most abundant deposition generally occurs within 10 km around emission sources, which can result in high local concentrations of lead in dust, soil and ambient water (Yankel et al., 1977).

Concentrations in ambient air have declined over the last decade as a result of the phasedown of leaded gasoline production and use, and reductions in emissions from stationary sources (U.S. EPA, 1989a).

3.2.2. Lead in Soil. Lead released to the air deposits on terrestrial surfaces and enters the soil, where it can have several possible fates. Lead can be retained in organic complexes near the soil surface. For example, insoluble lead species may be free or complexed metals adsorbed on solid inorganic or organic matrices. Studies of lead/soil interactions show that soil fixation of lead is mainly affected by pH, cation exchange capacity and organic matter content of soil. While it is true that, in a variety of soils, lead appears most strongly asociated with soil organic carbon fraction (Zimdahl and Skogerboe, 1977), no correlation is seen between organic content and lead concentrations in "brown soils" (Wojcikowska-Kapusta and Turski, 1986). In addition, if little or no organic content is in the soil, other components can regulate lead fixation. These include hydrous manganese oxide (Forstner et al., 1981) and hydrous ferric oxide (Swallow et al., 1980). Levels of lead in rural soils, away from industrial emissions and roadbeds, range from 5-30 µg lead/g soil (see Table 3-1). Levels of lead near roadbeds can be much higher

(30-2000 µg/g) and will vary with past and present traffic density and vehicle speed (Page and Gange, 1970; Quarles et al., 1974; Wheeler and Rolfe, 1979). Much higher levels (>30,000 µg/g) can occur in the immediate vicinity of industrial point sources (Yankel et al., 1977; U.S. EPA, 1986b).

Lead in urban soils includes lead from automotive and industrial emissions, as well as from leaded paints. Levels >2000 µg/g have been reported in soil around wood-frame houses painted with leaded paint (Ter Haar and Aronow, 1974; Mielke et al., 1983).

Lead bound to organic constituents in soil can remain in soil for long periods of time. As a result, elevated levels can persist long after sources of deposition have been reduced (Prpic-Majic et al., 1984).

3.2.3. Lead in Dust. Dust is an important source of oral lead intake in infants and children. The term "dust" refers to house and outdoor dust; house dust is dust in the interior of the building and includes such things as material for fabrics (carpet), and in paint and soil tracked or blown into the house. Outdoor dust includes anthropogenic materials deposited on outside surfaces, referred to as "street dust," and the mobile uppermost layer of natural soil, referred to as "soil dust" (U.S. EPA, 1986b). Atmospheric lead from automotive and industrial emissions are the primary contributors to outdoor dust. Paint can also be a significant source of outside dust around buildings painted with lead-based paint. Levels of lead in outdoor dust vary with proximity to emission sources and meteorological variables (Roels et al., 1980; Brunekreef et al., 1981; Yankel et al., 1977). Outdoor dusts can be transported by wind and rain runoff (Laxen and Harrison, 1977).

Lead in house dust can be derived from atmospheric deposition, transport of outdoor dust and deterioration of lead-based paint surfaces. Lead levels in house dust are determined by a number of factors including house cleaning practices, the presence and condition of lead-based paint surfaces, the presence of upholstered furniture and carpet, the amount of dust and soil transported into the house, the permeability of the house to outdoor air and the outdoor air lead concentration (U.S. EPA, 1986b). Lead can also enter the house through contaminated clothing worn by parents (CDC, 1989).

Lead in dust is relatively mobile. Levels in outdoor dust near point sources have been shown to decline within 1-2 years after atmospheric emissions decreased (Morse et al., 1979; Prpic-Majic et al., 1984).

3.2.4. Lead in Diet. Anthropogenic sources of lead in food include 1) deposition of atmospheric lead onto crops, forage, feed, soils and water; 2) lead-based pesticides; and 3) harvesting, processing, transportation, packaging, preparation and storage of food during which lead can enter the food by atmospheric deposition or leaching from metal containers and plumbing. Based on data from numerous studies of food consumption patterns and lead levels in various foods (U.S. FDA, 1983, 1984), the U.S. EPA developed a "Multiple Source Food Model" that establishes reference values for lead contents of typical diets for children and adults (U.S. EPA, 1986b). Declines in atmospheric emissions from automobiles and industrial point sources, in lead levels in water and in the use of lead solder in food containers are expected to result in declining levels of lead in food (U.S. EPA, 1989a; Cohen, 1988a,b).

3.2.5. Lead in Water. Lead can enter ambient water from atmospheric deposition and surface runoff, where it tends to form insoluble salts and precipitates. Concentrations of lead in U.S. ambient water are typically

low. Mean values tend to be ≤3-28 µg/ℓ (NAS, 1980; U.S. EPA, 1986b). In contrast to ambient water, levels in drinking water can be much higher (10-1000 µg/ℓ) because of leaching of lead from lead pipe and leaded solder joints. Lead concentrations in drinking water vary with the amount of lead in the household plumbing and corrosiveness of the water. Soft or acidic waters tend to be more corrosive and promote higher concentrations of dissolved lead in the drinking water (Worth et al., 1981). Drinking water can be a major source of lead intake for infants and young children who consume large amounts of infant formula prepared with household water.

3.2.6. Lead in Paint. Ingestion of lead-based paint is one of the most frequent causes of severe lead intoxication in children (Chisolm, 1984). Although the U.S. Consumer Product Safety Commission banned the use of household paints containing >0.06% lead in 1977, the hazard persists in homes and apartments constructed before the ban. In homes built before 1940, some interior paints contained >50% lead. An estimated ≈20% of housing units built between 1960 and 1974 have lead paint levels >0.7 mg/cm^2 (ATSDR, 1988).

Infants and children are exposed to lead in paint from ingesting and inhaling house dust contaminated with lead and from ingesting paint chips (paint pica). Exposure can occur outside the house from ingestion of street and soil dust. Exposure is higher in houses with deteriorating surfaces (e.g., peeling of paint, cracked plaster). In 1980, an estimated 6.2-13.6 million children under the age of 7 years resided in housing containing lead-based paint; 235,000-842,000 children resided in homes with deteriorating surfaces (Pope, 1986; ATSDR, 1988). Since exposure to lead in paint is unrelated to atmospheric, soil or dietary levels of lead, efforts to

reduce lead levels in these media will have little impact on the incidence of lead intoxication associated with lead paint.

3.3. MEDIA-SPECIFIC ESTIMATES FOR DIFFERENT LEVELS OF LEAD UPTAKE

Biokinetic models currently exist that predict age-specific blood lead levels associated with age-specific uptake rates (Harley and Kneip, 1985). This section discusses the major quantitative factors that must be incorporated into predictions of lead uptakes from specific environmental media. Default assumptions and reference values incorporated into an Uptake/Biokinetic Model for lead (described in Section 4.1.) are also discussed. In most populations, lead uptake occurs primarily as the result of intake of lead in air, diet, drinking water and dust; therefore, the discussion is confined to these media. Intake of leaded paint chips can contribute significantly to uptake in infants and children living or playing in areas contaminated with lead paint.

Uptake (U_i) of lead from a given exposure medium can be thought of as the product of two separate processes, intake (I_i) and absorption (A_i):

$$U_i = I_i \cdot A_i$$

where intake (I_i) is the product of the concentration of lead in specific media and the rate for the physiological mechanism of intake (e.g., breathing rate).

Predictions of media-specific lead uptakes must take into account environmental fate processes that determine concentrations of lead in relevant media (see Section 3.2.), as well as behavioral and physiological factors that affect intake and absorption from these media.

3.3.1. Uptake from Ambient Air. Humans are exposed to lead in indoor and outdoor air. Uptake rates will be determined by the lead concentrations in

indoor and outdoor air, the time spent indoors and outdoors and physiological determinants of deposition and absorption in the respiratory tract. A simple mathematical expression for this relationship is as follows:

$$U_A = V \cdot DA \cdot [Pb]_{TWA}$$

where U_A is uptake from air (μg/day), V is the volume of air breathed/day (m^3/day), DA is the product of the respiratory deposition and absorption fractions and $[Pb]_{TWA}$ is the time-weighted average exposure concentration (μg/m^3).

3.3.1.1. INDOOR AND OUTDOOR AIR LEAD — As discussed in Section 3.3.1., numerous factors determine the concentration of lead in air at any given location. These include distance and direction from emission sources, the nature of the source and meteorological patterns that affect dispersion and deposition of airborne lead. Many of these factors have been incorporated into predictive models of airborne particulate dispersion, which can be used to predict air lead levels associated with a given location near a point source (U.S. EPA, 1986c).

Transport of lead from outdoors to indoors accounts for virtually all indoor air lead in most modern buildings. Outdoor air lead enters buildings through windows, doors, walls and air vents. Because the transport processes are complex, relationships between outdoor and indoor air lead concentrations can be expected to vary from site to site. Factors that can be expected to affect indoor/outdoor ratios at a given site include the proximity to emission sources, which determines the size of outdoor air lead particles, the permeability of entrance pathways (e.g., windows, doors, walls) to lead, airflow patterns in and out of the building and meteorological conditions.

U.S. EPA (1986b) summarized data on indoor and outdoor air lead levels and concluded that, at most sites, outdoor concentrations exceeded indoor concentrations. Indoor/outdoor concentration ratios ranged from 0.3-0.8, with values in the lower end of the range near point sources, where lead particles are larger (Cohen and Cohen, 1980).

3.3.1.2. TIME SPENT OUTDOORS — An estimate of daily exposure to lead must be a time-weighted average of exposure to outdoor and indoor lead; therefore, information on the relative amount of time spent in each environment is required to estimate average exposure levels. Time spent outdoors varies extensively with age, season, geographical location and a variety of cultural and behavioral influences. The following age-specific estimated ranges for hours spent outdoors were derived from a literature review (U.S. EPA, 1989a) summarized in Pope (1985) and reflect data reported in various studies (Hoffman et al., 1979; Rubinstein et al., 1972; Suter, 1979; Koontz and Robinson, 1982):

Age (years):	0-1	1-2	2-3	3-7
Time Outdoors (hours/day):	1-2	1-3	2-4	2-5

Based on information on indoor and outdoor air lead concentrations and the average time spent outdoors and indoors, an estimate of the time-weighted average exposure concentration ($[Pb]_{TWA}$) can be calculated as follows:

$$[Pb]_{TWA} = ([Pb]_{Ao} \cdot T_o) + ([Pb]_{Ai} \cdot Ti) \cdot (1/24)$$

where $[Pb]_{Ao}$ and $[Pb]_{Ai}$ are outdoor and indoor air concentrations ($\mu g/m^3$), respectively, and T_o and T_i are average times (hours/day) spent outdoors and indoors.

3.3.1.3. INHALATION AND RESPIRATORY DEPOSITION AND ABSORPTION — Intake of lead in air is determined by the volume of air breathed each day, which varies with age, body size and level of physical activity (U.S. EPA,

1989c). Age-specific estimates of daily breathing volumes have been derived (Phalen et al. 1985), from which the following reference values for daily breathing volumes in children were developed (U.S. EPA, 1989a):

Age (years):	0-1	1-2	2-3	3-4	4-5	5-6	6-7
Daily Volume (m^3/day):	2-3	3-5	4-5	4-5	5-7	5-7	6-8

The fraction of inhaled lead that is deposited and absorbed varies with airborne particle size and age (Chan and Lippmann, 1980; Phalen et al., 1985; Xu and Yu, 1986). As is described in Section 2.2.1.1. (see Tables 2-1 and 2-2), age- and particle-size-specific references values for these parameters have been derived from existing experimental data.

3.3.2. Dietary Lead Uptake. Uptake of lead from the diet (U_D) can be expressed as follows:

$$U_D = I_D \cdot A_D$$

where I_D (µg Pb/day) is the intake from dietary sources and A_D is the fractional gastrointestinal absorption (absorption coefficient) of dietary lead. Dietary food intake can be estimated from historical data on food lead content (U.S. FDA, 1983, 1984) and data on food consumption (Pennington, 1983). A Multiple Source Food Model has been developed that partitions dietary sources into three major categories: 1) metallic sources including lead solder in food cans and solder or pipe in drinking water systems; 2) atmospheric lead deposited on food before and after harvest and processing; and 3) sources for which an origin has not been established (U.S. EPA, 1986b). These classifications allow projections for dietary intake based on projected adjustments in each category (e.g., a reduction in atmospheric lead) (Cohen, 1988a,b). Projections for 1990 are presented in Table 3-2.

Absorption of dietary lead varies with age, diet and nutritional status (see Section 2.2.1.2.). Absorption is an estimated 42-53% in infants

TABLE 3-2

Age-Specific Estimates of Total Dietary Lead Intake for 1990-1996 (μg/day)*

Age (years)	Metallic	Atmospheric	Other	Total
<1	3.4	0.8	3.3	7.5
1	4.0	1.1	3.8	8.9
2	5.6	1.2	3.6	10.4
3	5.8	1.2	3.7	8.9
4	5.9	1.1	3.8	8.9
5	6.1	1.2	4.0	9.3
6	6.3	1.3	4.3	9.8

*Source: Cohen, 1988a,b

(Alexander et al., 1973; Ziegler et al., 1978) and 7-15% in adults (Kehoe, 1961a,b,c,; Chamberlain et al., 1978; Rabinowitz et al., 1980). There is some evidence that gastrointestinal absorption of lead may be a nonlinear process (Aungst and Fung, 1981; Marcus, 1989). Saturable and nonsaturable absorption mechanisms have been described for essential metals; thus, it is reasonable to expect the existence of saturable and nonsaturable mechanisms for lead. Kinetic constants for saturable lead absorption have been experimentally determined in the in vitro everted rat intestine (Aungst and Fung, 1981). The apparent Km for flux through the everted intestine was reported to be ≈125 µg/L, which is substantially higher than the concentration of lead in the intestine that can be expected to occur from average dietary intake (<25 µg/L). However, other dietary metals may compete with lead for saturable absorption mechanisms (e.g., carrier-mediated transport); therefore, the contribution of saturable mechanisms to total absorption may depend on diet, nutritional status and the relative magnitude of the Kms for each substrate for the saturable mechanism. Kinetic constants for saturable lead absorption have not been determined in primates.

3.3.3. Uptake from Dust and Soil. Children are exposed to lead in indoor and outdoor dust and soil, primarily from ingesting these materials as a result of normal mouthing behavior and pica (abnormal tendency to ingest nonfood materials). Thus, the average daily exposure will be determined by lead levels in each medium and amounts of each medium that are ingested daily. The latter may vary with age, season, geographic location and activity patterns. A simple expression for lead uptake from dust and soil (U_{DS}) is as follows:

$$U_{DS} = DS_{ING} \cdot A_{DS} \cdot [Pb]_{DS}$$

where DS_{ING} is oral intake of dust and soil (g dust and soil/day), A_{DS} is the absorption fraction and $[Pb]_{DS}$ is the average exposure level (µg Pb/g dust and soil).

3.3.3.1. LEAD LEVELS IN DUST AND SOIL — As discussed in Sections 3.2.2. and 3.2.3., levels of lead in dust and soil are determined by a variety of factors related to the exposure source, meteorological conditions, transport of dust into the home and sources of lead in and around the home (i.e., lead paint). The most desirable quantitative estimates for localized areas should result from adequate soil and dust monitoring data. However, it is important that sufficient monitoring data are collected from different local sites to produce meaningful average (mean) lead concentrations. Since the lead concentration in soil may vary significantly between samples collected in the same area, the use of a single sample to estimate lead exposure to children may result in inaccurate estimation of ingested lead uptakes.

In the absence of sufficient monitoring data, the geometric mean lead concentration of soil and dust can be estimated from average lead concentration in the air using linear relationships described in Appendix B of the U.S. EPA (1988a). This applies only to situations in which current air lead is the primary source for soil lead. The derivation of these relationships include the following assumptions: 1) changes in the air concentration will be followed by corresponding changes in soil lead and interior house dust lead concentrations; 2) the rate at which lead enters soil/dust is constant and equal to atmospheric deposition (plus other inputs) minus soil removal; and 3) the environmental lead emissions have been nearly constant for a sufficiently long time that lead levels in soil and dust are in dynamic equilibrium. The derivation of the linear relationships does not consider

many complex variables that can affect air/soil relationship for lead, such as chemical and physical properties of the lead particles and soil, topographic and meteorological conditions, and the frequency of precipitation and washing of streets and interior surfaces.

The coefficients of the linear equations used to estimate soil/dust lead from air lead were determined from monitoring data collected at sites where both air lead levels and dust and surface soil concentrations were measured and averaged over varying periods of time. The data used to determine the coefficients were collected near lead point sources where emissions were comparable with current lead exposure situations and lead contributed by new houses and factories. Figure 3-2 is a log-arithmic plot of average air concentration versus average soil concentration for the data used in the coefficient determinations for soil lead; the data are described in Appendix A of the U.S. EPA (1988a). The raw data are fitted after a log transformation to yield geometric mean concentrations and the following linear equations (U.S. EPA, 1989a):

$$\text{Log Soil Lead} = a + b \cdot \text{Log Air Lead}$$

$$\text{Log Dust Lead} = c + d \cdot \text{Log Air Lead}$$

where the coefficients a, b, c and d are 50.1, 579.0, 57.6 and 972.0, respectively. The current Uptake/Biokinetic Model (Section 4.1.2.) uses slightly modified coefficients of 53, 510, 60 and 844, respectively (Section 4.1.1.). The above equations were based on monitoring data for point source sites such as smelters; however, the relationship between air lead and soil and indoor dust lead may vary, depending on the lead emission source. For example, mining sites with no history of smelter activity represent a situation where indoor dust concentrations of lead are not greater than concentrations in outdoor soil. Review of actual measurements of soil and

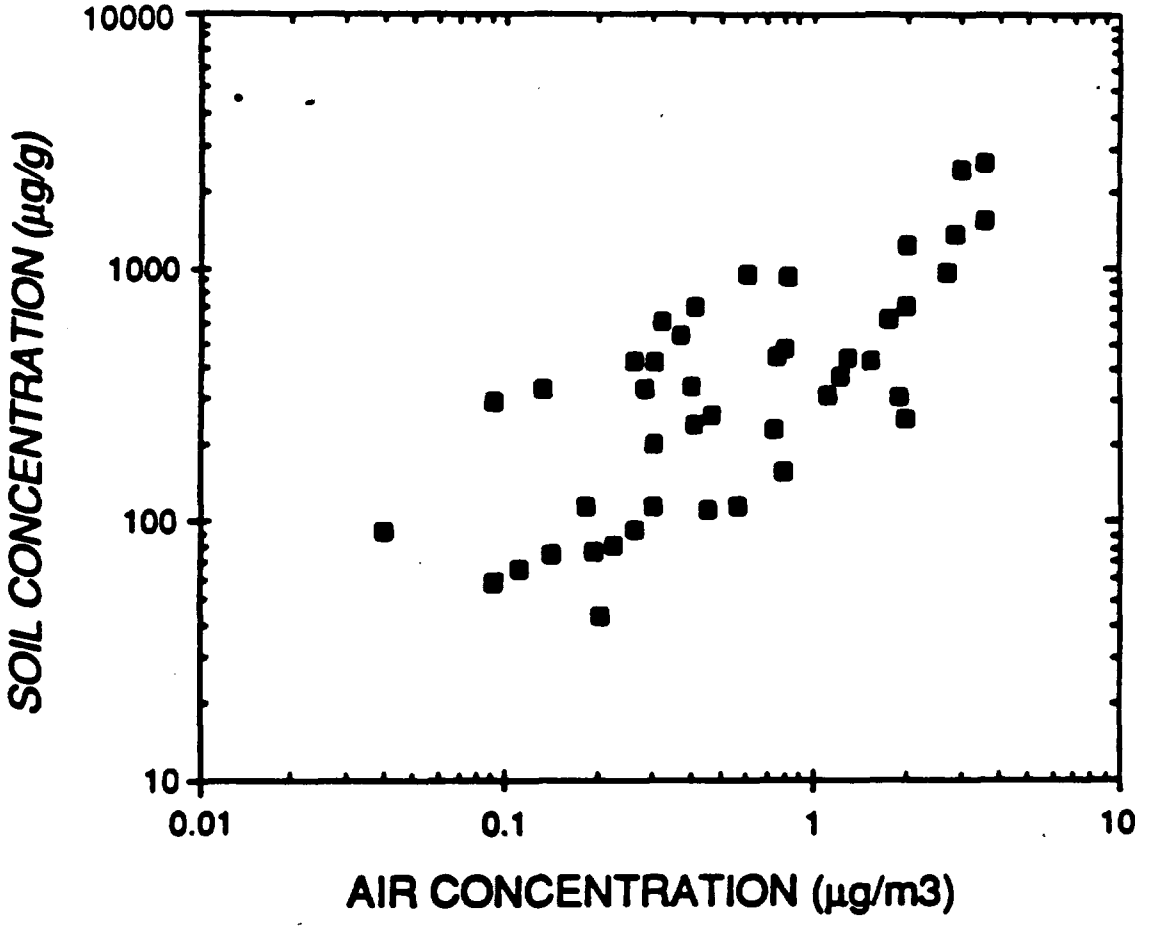


FIGURE 3-2

Plot of Soil Lead Concentration vs. Air Lead Concentration Monitored in Various Locations

Source: U.S. EPA, 1986b

house dust lead reported at mining sites indicated that, when soil lead was <500 ppm, house dust lead concentrations were usually greater than soil lead, indicating the greater contribution of indoor sources of lead. However, when soil lead was >100 ppm, house dust lead concentrations ranged from 18-48% of soil lead concentrations (Steele et al., 1989).

The use of the linear equations to estimate soil and dust lead levels near primary and secondary lead smelters may underestimate current exposure because of historical accumulations of relatively large particles at these sites, regardless of current emissions controls (U.S. EPA, 1989a). These sites will probably require separate estimates for current soil and dust levels.

The data on the time scales for soil and dust lead changes do not lead to definite conclusions (U.S. EPA, 1989a). The current opinion is that lead in undisturbed soil matrix persists for an extremely long time; however, soil lead concentrations in disturbed (especially urban) environments will change, on average, over periods of a few years to reflect changes in surface deposition (U.S. EPA, 1989a). Although lead does deposit on the surface of soils, significant lead concentrations have been found down to 12 inches below the surface. This indicates that human activities such as gardening and new building construction can result in significant concentrations of atmospherically deposited lead in deeper soils. Interior dust lead concentrations will likely change over periods of weeks to months in response to air lead changes, depending on interior-exterior access and interior recirculation or removal of dust as well as the primary sources of dust and soil lead. Sources such as lead paint dust, mine-tailing and smelters that have ceased to operate may continue to contribute lead to soil and dust regardless of changes in air lead.

The linear equations yield approximations based upon the best available monitoring data and interpretations, but do not consider various complex variables that may significantly affect soil and dust concentrations. The use of adequately measured soil and dust concentrations is preferable to use of the linear equations. However, in the absence of appropriate measurement data, application of the linear equations in the Uptake/Biokinetic Model can yield reasonable initial approximations.

3.3.3.2. INTAKE OF DUST AND SOIL — Infants and children ingest soil and dust as a result of hand-to-mouth activity, consumption of food items that have been in contact with dust and soil, and soil pica. Considerable age-related and individual variation can be expected in these activities. Hand-to-mouth activity reportedly occurs in ≈80% of children 1-2 years old, and pica in ≈5% of children at this age; both activities decline in years 3-6 (Millican et al., 1962; Barltrop, 1966).

Estimates of soil and dust intake in children have been derived from measurements of the fecal excretion of poorly absorbed soil minerals (e.g., aluminum, silicon and titanium) (Binder et al., 1986; Clausing et al., 1987; Calabrese et al., 1989). A mass balance equation used to calculate soil ingestion (I_S) is as follows:

$$I_S = ((([M]_F \cdot F)/EF) - I_D)/[M]_S$$

where $[M]_F$ is the concentration of the mineral in feces (mg/g feces), F is the amount of feces excreted each day (g/day), EF is the fraction of ingested mineral that is excreted in the feces, I_D is the dietary intake of the mineral (mg/day) and $[M]_S$ is the concentration of the mineral in soil (mg/g). The above estimates can be generalized to dust and soil (i.e., dirt), assuming that concentrations in dust are similar to concentrations in

soil. Estimates derived from this mass balance approach are subject to errors associated with estimates of gastrointestinal absorption and dietary intake of the mineral.

Sedman (1989) analyzed data on fecal mineral excretion (Binder et al., 1986), on mineral content of the diet and on food consumption in infants and young children (Pennington, 1983) to estimate soil ingestion for 1- to 3-year-old children. Estimates were 40, 70 and 640 mg soil/day based on mass balances for aluminum, silicon and titanium, respectively. Clausing et al. (1987) examined aluminum, silicon and titanium excretion in 18 nursery-school children and 6 hospitalized children, ages 2-4 years. Estimates of dietary intake of each mineral were based on measurements of fecal excretion of each mineral in the hospitalized children. The average estimated soil ingestion in the nursery school children for all three tracers was 56 mg soil/day. If the values for dietary intake from Clausing et al. (1987) are applied to the Binder et al. (1986) data on fecal excretion, estimates of soil ingestion range from 80-135 mg soil/day for 1- to 3-year-old children (U.S. EPA, 1989a).

Attempts to define reference values for dust and soil intake in children must take into account the range of soil pica that can occur in human populations. Children with high tendencies for soil pica may ingest 1000 times more soil than children with a low tendency for pica (Calabrese et al., 1987; U.S. EPA, 1989c). Based on an analysis of available studies (Binder et al., 1986; Clausing et al., 1987) and considerations of Calabrese et al. (1987), the following values for average daily dust and soil ingestion have been developed:

Age (years):	0-1	1-2	2-3	3-4	4-5	5-6	6-7
Intake (mg/day):	0.005	0.05	0.20	0.20	0.05	0.05	0.05

The above estimates may not apply to children with unusual tendencies for soil pica which can result in much higher intake of soil (Calabrese et al., 1989). Furthermore, the above values may be adjusted downwards in future revisions of the Uptake/Biokinetic Model. In a study recently brought to the attention of the U.S. EPA, Calabrese et al. (1989) demonstrated that failure to accurately measure fecal weight and to consider dietary intake of trace metals may result in overestimation of soil intake based on the measurements of the fecal content of trace metals. Calabrese et al. (1989) reported a range of 24-68 mg/day for dust and soil ingestion in children (1-4 years old) based on fecal excretion of aluminum, silicon and yttrium.

3.3.3.3. GASTROINTESTINAL ABSORPTION OF DUST AND SOIL LEAD — The greatest source of uncertainty in the prediction of lead uptake from dust and soil is the estimate of gastrointestinal absorption of lead. In vitro studies have shown that the lead in dust and soil is solubilized in acidic solutions similar to that found in the stomach; however, in alkaline solutions similar to intestinal fluids, lead can remain bound to soil (Day et al., 1979; Harrison, 1979; Duggan and Williams, 1977). Dietary balance studies have yielded estimates of ≈42% for gastrointestinal absorption of dietary lead in infants and children (see Section 2.2.1.2.); however, absorption efficiency may differ for lead in dust and soil.

Absorption of lead for dust and soil is influenced by three important factors: chemical species, particle size and concentration in soil. Chaney et al. (1988) demonstrated that absorption of lead for soil varies with lead concentration in soil.

Particle size also determines the degree to which lead is absorbed into the body; the larger the particle size, the less the absorption. For example, lead sulfide on larger particles eventually dissolves in gastric fluid to the same concentration as lead sulfide on smaller particles, but the process takes longer (100 vs. 200 minutes) (Healy et al., 1982). Thus, absorption may be less in the stomach for the larger particles because the particles do not remain in the stomach long enough to become completely solubilized. It is, therefore, very important when reviewing site-specific data to determine the prevalent particle size on which the lead is located. In some locations where lead contamination in soil is high, such as mining areas, the particle sizes are much larger than in other locations, such as smelter towns, possibly resulting in decreased bioavailability. Lead species is another critical factor in determining bioavailability. Barltrop and Meek (1979) reported that lead sulfide is significantly less absorbed than lead acetate and lead oxides.

The issue of bioavailability of lead for soil is a major source of uncertainty in the Uptake/Biokonetic Model and merits further investigation. Applying information on particle size, lead species and soil characteristics in bioavailability estimates would prove very useful in further validation of the model.

3.3.4 Uptake of Lead from Drinking Water. Uptake of lead from drinking water (U_W) can be expressed as follows:

$$U_W = I_W \cdot A_W$$

where IW (µg/day) is the intake from drinking water and A_W is the fractional absorption of ingested lead. Intake of lead from drinking water can be expressed as follows:

$$I_W = [Pb]_W \cdot W_{ING}$$

where $[Pb]_W$ (μg/ℓ) is the average daily concentration of lead in drinking water and W_{ING} is the average amount of drinking water ingested each day. The amount of drinking water ingested will vary with numerous factors including age, body size, diet, physical activity, ambient temperature and humidity. Using data collected by the U.S. Department of Agriculture in the 1977-1978 Nationwide Food Consumption Survey, average daily intake levels of drinking water have been derived (U.S. EPA, 1989c):

Age (years):	0-1	1-2	2-3	3-4	4-5	5-6	6-7
Ingestion (ℓ/day):	0.20	0.50	0.52	0.53	0.55	0.58	0.59

3.4. ENVIRONMENTAL EXPOSURE LEVELS ASSOCIATED WITH BLOOD LEAD LEVELS

In the previous section, strategies for predicting uptake rates from specific media (air, diet and dust/soil) were described, which, in conjunction with biokinetic models, provide the basis for predicting relationships between media-specific exposure levels and blood lead levels. An alternative approach is to derive mathematical descriptions of these relationships from the analysis of human experimental and epidemiological data on environmental exposure levels and blood lead. This section provides an overview of the existing information on relationships between levels in various media and blood lead levels in humans. A more comprehensive discussion is presented in other Agency documents (U.S. EPA, 1986b, 1989a).

3.4.1. Blood Lead/Air Lead Relationships. The relationship between air concentration and blood lead level in human populations reflects uptakes directly from air by inhalation as well as oral uptakes of atmospheric lead deposited on dust, soil, food and water. Several studies have provided data on air lead levels and blood lead in human populations from which slope factors (blood lead/air lead) can be derived (Landrigan et al., 1975; Roels et al., 1976; Yankel et al., 1977; Morse et al., 1979; Angle and McIntire,

1979; Brunekreef, 1984). The aggregate slope factors, reflecting the combined impact of air lead uptake from all media on blood lead, range from 2-20 (μg/dℓ)/(mg/m^3) in young, moderately exposed children (U.S. EPA, 1986b, 1988a).

Experimental studies in which changes in blood lead levels are measured in human subjects exposed to lead aerosols yield estimates of slope factors (blood lead/air lead) for inhaled air lead. Several experimental studies of adults have been reported (Kehoe, 1961a,b,c; Griffin et al., 1975; Rabinowitz et al., 1974, 1976, 1977; Chamberlain et al., 1978). The pooled weighted estimate of the slope for the relationship between blood and air lead for all of the studies is 1.64±0.22 (S.E.) (μg/dℓ)/(mg/m^3), and 1.9 (μg/dℓ)/(mg/m^3) if subjects that were exposed to very high lead levels (≥36 μg/dℓ) in the Kehoe studies are excluded (U.S. EPA, 1986b; 1988a).

Analysis of cross-sectional data of blood lead/air lead relationships in human populations can yield estimates of disaggregate blood lead/air lead slope factors, reflecting the relationship between inhaled lead and blood lead in the population, if information on noninhalation sources of exposure is sufficiently documented. Several studies in adult human populations have been reported (Azar et al., 1975; Tepper and Levin, 1975; Nordman, 1975; Johnson et al., 1975). In these studies, various approaches are used to account for nonair lead exposures. The range for blood lead/air lead slopes are 1-2 (μg/dℓ)/(mg/m^3) (U.S. EPA, 1986b).

The EPA analyzed three studies of blood lead/air lead relationships in children (U.S. EPA, 1986b). Estimated air disaggregate blood lead/air lead slopes (μg/dℓ)/(mg/m^3) for the three studies are 1.92±0.60 (Angle and

McIntire, 1979), 2.46±0.58 (Roels et al., 1980) and 1.53±0.84 (Yankel et al., 1977; Walter et al., 1980); the median slope is 1.97 (μg/dℓ)/(mg/m^3).

3.4.2. **Blood Lead/Dust and Soil Lead Relationships.** Few studies have provided data on blood lead levels in children and levels in local soil and dust, from which blood lead/dust lead and blood lead/soil lead slope factors can be estimated (Barltrop et al., 1975; Yankel et al., 1977; Neri et al., 1978; Angle and McIntire, 1982; Stark et al., 1982). The range of mean slope factors is 0.6-6.8 (μg/dℓ)/(mg Pb/g) soil (U.S. EPA, 1986b). The range for blood lead/house dust lead slope is 0.2-7.2 (μg/dℓ)/(mg Pb/g) dust (Stark et al., 1982; Yankel et al., 1977; Angle and McIntire, 1979). Blood/soil lead slope factors vary, depending on the nature of source of lead. For example, the average slope for mining sites is an estimated 1.7 μg/dℓ/mg Pb/g soil, whereas the average slopes for urban and smelter sites were 3.2 and 4.2, respectively (Steele et al., 1989).

3.4.3. **Blood Lead/Diet and Drinking Water Lead Relationships.** The U.S. EPA (1986a) has summarized studies relating dietary intake and blood lead levels. The relationships appear to be nonlinear at dietary intakes >200 μg Pb/day. When data are compared over the range of 100-200 μg dietary Pb/day, blood lead/dietary lead slope factors ranging from 0.034-0.16 can be obtained (Stuik, 1974; Cools et al., 1976; Schlegel and Kufner, 1979; Kehoe, 1961a,b,c; U.K. Directorate, 1982; Sherlock et al., 1982; Ryu et al., 1983).

The relationship between blood lead level and drinking water level is nonlinear at water concentrations >100 μg Pb/ℓ water. The U.S. EPA (1986b) concluded that the best estimate for the slope factor associated with first draw water concentrations <100 μg/ℓ was 0.06 (μg Pb/dℓ

blood)/(μg Pb/ℓ water) (Pocock et al., 1983). More recent analysis of the relationship of blood lead and drinking water level supports the slope factor of 0.2-0.25 (μg lead)/(dℓ blood)/(μg lead/ℓ) water for infants and children (U.S. EPA, 1988b).

3.5. SUMMARY

The primary source of environmental lead is atmospheric emissions from automobiles and industrial point sources that ultimately deposit in dust, soil, ambient water and food. Infants and children appear to be the most vulnerable segments of the population to environmental lead, because, in addition to inhaling airborne lead and ingesting dietary lead, they tend to ingest dust and soil as part of their normal behavior. Indeed, oral ingestion of dust and soil can be the predominant uptake mechanism in infants and young children. These same behavioral tendencies place them at risk for ingesting lead-based paint chips.

The biological effects of lead in infants and children have been related to blood lead levels, which are determined by the combined uptakes from the respiratory and digestive tracts. Uptake from both routes can be expected to vary appreciably with the nature and proximity of the exposure source, as well as age-related physiological variables that influence intake and absorption efficiency.

Although dust, soil and dietary lead are largely derived from atmospheric deposition, simple relationships between airborne lead concentrations and blood lead levels useful for deriving age-specific and media-specific risk assessments are not available. However, media- and age-specific uptakes can be predicted using a multimedia uptake assessment model, given certain assumptions regarding the nature and proximity to the

exposure source, levels of lead in each media, and behavioral and physiological variables that influence intake and absorption. A biokinetic model can then be used to predict age-specific blood lead levels associated with multimedia uptakes. This multimedia Uptake/Biokinetic Model approach is described in greater detail in Chapter 4.

4. RISK CHARACTERIZATION

4.1. INTEGRATED LEAD UPTAKE/BIOKINETIC EXPOSURE MODEL

This section describes an Uptake/Biokinetic Model that estimates age-specific blood lead levels associated with levels of continuous exposure to air, dietary, drinking water, dust/soil and paint lead sources. The uptake model accepts site-specific data or default values for lead levels in each medium. This information is combined with assumptions regarding behavioral and physiological parameters that determine intake and absorption of lead from each medium to yield estimated rates of lead uptake into the blood. Behavioral and physiological parameters are adjusted for different ages and include such items as: time spent indoors and outdoors; time spent sleeping; diet; dust/soil ingestion rates; daily breathing volumes; deposition efficiency in the respiratory tract; and absorption efficiency in the respiratory and gastrointestinal tracts.

The biokinetic model accepts uptake predictions and computes age-specific blood lead levels based on a six-compartment biokinetic model of tissue distribution and excretion of lead. The model incorporates default assumptions regarding rate constants for transfers between blood and four physiological compartments: bone, kidney, liver and gastrointestinal tract. Transfers from blood to urine, liver to the gastrointestinal tract and mother to fetus are considered, as well. These assumptions include adjustments that reflect age-related changes in metabolism and physiology that affect the distribution and excretion of lead (e.g., bone turn-over rates). The Uptake/Biokinetic Model sums predicted uptakes over time to yield estimates of blood lead levels associated with continuous uptakes over the lifespan.

The uptake/biokinetic approach is extremely versatile and flexible in that age-specific predictions can be made for multimedia exposures. Uptake from all sources by all absorption routes can be separately modeled. This provides an estimate of the relative impact of changes in levels of specific media on blood lead levels. The default assumptions and values on which uptake rate and blood lead calculations are based can be replaced with site-specific data or revised defaults. Thus, the model can be updated as new information on exposure level, intake and uptake parameters become available. This can be used to explore predictions regarding the impact of future trends in environmental lead levels resulting from proposed control efforts and regulations.

4.1.1. Estimates of Lead Uptake. Presented in Table 4-1 is the calculation scheme for deriving estimates of lead uptakes from four primary routes of exposure to environmental lead: inhaled air lead, lead in the diet, level in drinking water and lead in dust/soil. A separate calculation is presented for each of three air lead levels (25, 50 and 100 $\mu g/m^3$) to demonstrate how medium-specific uptake rates vary with changes in air lead. For illustration, uptakes are calculated for 2- to 3-year-old children (24-36 months of age) who were not exposed to lead paint. However, the model will accept estimates of intake from ingestion of lead in paint. This is discussed further in Section 4.1.2.

Formulas and default assumptions for each step in the uptake calculations are enumerated below (numbers refer to computational and input steps in Table 4-1).

1. Air lead. The exposure concentrations ($\mu g/m^3$) are inputs to the model. These can consist of site monitoring data or predictions based on site-specific source analysis such as those derived from the Industrial

TABLE 4-1

Lead Intake and Uptake in 2- to 3-Year-Old Children Exposed to Lead in Air, Diet, Dust, Soil and Drinking Water*

Input Parameter or Calculation	0.25	0.50	1.00
1. Air lead (μg/m³)	0.25	0.50	1.00
2. Breathing volume (m³/day)	5	5	5
3. Lead intake from air (μg/day)	1.25	2.5	5.0
4. % respiratory deposition/absorption	32	32	32
5. Total lead uptake from inhaled lead (μg/day)	0.4	0.8	1.6
6. Dietary lead intake (μg/day)	29	29	29
7. % gastrointestinal absorption	50	50	50
8. Dietary lead uptake (μg/day)	14.5	14.5	14.5
9. Outdoor soil lead (μg/g)	180	308	563
10. Indoor dust lead (μg/g)	271	482	904
11. Amount of dust and soil ingested (g/day)	0.2	0.2	0.2
12. Weighting factors (soil/dust)	0.45-0.50	0.45-0.50	0.45-0.50
13. Lead intake from dust and soil (μg/day)	46	81	150
14. % gastrointestinal absorption	30	30	30
15. Lead uptake from dust and soil (μg/day)	13.8	24	45
16 Drinking water lead (μg/ℓ)	9	9	9
17. Drinking water intake (ℓ/day)	0.5	0.5	0.5
18. Drinking water lead intake (μg/day)	4.5	4.5	4.5
19. % absorption of lead from drinking water	50	50	50
20. Drinking water lead uptake (μg/day)	2.3	2.3	2.3
21. Total lead uptake from respiratory and gastrointestinal tract (μg/day)	31	41	63

*Children living near one or more lead point sources and unaffected by lead paint

Source Complex Dispersion Model (U.S. EPA, 1986c). Since children may be exposed to lead in both outdoor and indoor air, exposure concentrations should reflect time-weighted averages of exposure to both environments. The time-weighted exposure level will be highly dependent on the amount of time children spend outdoors. Activity patterns of children vary considerably with age, season, geographic location and cultural factors. Therefore, in estimating time-weighted average exposure concentrations, these factors should be characterized in the population of interest. Computational strategies for estimating time-weighted exposure concentrations are discussed in Sections 3.3.1.1 and 3.3.1.2.

2. Breathing volume. The model uses a default value of 5 m^3/day for the average daily breathing volume of 2- to 3-year-old children. However, as discussed in Section 3.3.1.3, breathing volume may vary considerably from this value, depending on body size and physical activity.

3. Lead intake from breathing air. Intake from breathing (I_A) is calculated as follows:

$$I_A = V \cdot [Pb]_A$$

where V is the daily breathing volume (m^3/day) and $[Pb]_A$ is the exposure concentration ($\mu g/m^3$). Intake is calculated for the 0.25 $\mu g/m^3$ exposure concentration as follows:

$$\text{lower limit} = (4\ m^3/day)(0.09\ \mu g/m^3) = 0.4\ \mu g/day$$

$$I_A = (5\ m^3/day)(0.25\ \mu g/m^3) = 1.25\ \mu g/day$$

4. Respiratory deposition/% absorption of inhaled lead. As discussed in Section 2.2.1.1., the deposition and absorption efficiencies of particles in the respiratory tract vary with particle size, which can be expected to

relate to the nature of and proximity to the exposure source. The model uses a default value of 31.5% for the estimated percent absorption of inhaled lead particles for 2- to 3-year-old children.

5. Total lead uptake from inhaled lead. Total lead uptake from inhalation of airborne lead (U_A, µg/day) is calculated using the equation in Section 3.3.1:

$$U_A = I_A \cdot DA$$

where I_A is the intake of airborne lead by the respiratory tract (µg/day) and DA is the product of the respiratory deposition and absorption fractions. For the example presented in Table 4-1 in which air lead is assumed to be 0.25 $\mu g/m^3$, the uptakes are calculated as follows:

$$U_A = (1.25 \text{ µg/day})(0.32) = 0.4 \text{ µg/day}$$

6. Dietary lead intake. As discussed in Section 3.3.2., typical dietary lead intakes for each age group are defined from the results of Market Basket Surveys and analyses of food lead content (U.S. FDA, 1983, 1984; Pennington, 1983). For the purpose of making projections in time- or site-specific estimates, a Multiple Source Food Model is used to partition dietary sources (including water) into three categories: 1) metallic, including lead from solder joints and pipes in plumbing and solder in food cans; 2) atmospheric, including deposition of atmospheric lead on food before or after harvest, or during processing; and 3) other sources. Default projections for the typical diet of children during the years 1990-1996 are presented in Table 3-2.

The values presented in Table 4-1 are based on data from dietary surveys completed in 1986. However, current dietary levels may be lower because of decreases of lead in canned food (Cohen, 1988a,b). Strategies for

projecting survey data forward in time to account for these changes are discussed in Section 3.3.2.

In the example presented in Table 4-1, the default projections do not change with increasing air lead. The basis for this assumption is that the typical U.S. diet consists of foods harvested and processed in diverse geographical locations. Thus, atmospheric contributions are not likely to be related to local air lead levels. Exceptions to this can be anticipated. For example, in rural areas where consumption of home-grown vegetables is common, local air lead levels may be an important determinant of dietary intake. In this case, site-specific estimates of dietary intake or adjustments to the atmospheric source category would be used in the model in place of default values. The model accepts data on the concentrations of lead in home-grown fruits and vegetables, locally harvested fish and game animals, and data on the estimated portion of the diet derived from each food category. This information is incorporated into the calculations of dietary and total lead uptakes.

7. <u>% Gastrointestinal absorption of dietary lead</u>. Gastrointestinal absorption of lead is assumed to occur by nonsaturable (passive) and saturable (active) mechanisms. The absorption coefficient (A_D) at any given dietary intake is, therefore, the sum of the passive absorption coefficient (A_DP) and the active absorption coefficient (A_DA), factored by the concentration for lead in the gastrointestinal tract and the apparent Km for active absorption, as follows:

$$A_D = A_{DP} + (A_{DA}/(1+([Pb]_{GI}/Km)^3))$$

where:

A_D = dietary absorption coefficient;
A_{DP} = coefficient for nonsaturable (passive) absorption;
A_{DA} = coefficient for saturable (active) absorption;
$[Pb]GI$ = concentration of lead in the gastrointestinal tract (µg/ℓ); and
Km = apparent Km for saturable absorption (µg/ℓ).

The default values for 2- to 3-year old children that are used in the model are as follows:

A_D = 0.5 for the default dietary intake of 29 µg/day;
A_{DP} = 0.15;
A_{DA} = 0.35 for the default dietary intake of 29 µg/day;
$[Pb]_{GI}$ = 12 µg/ℓ for the default dietary intake of 29 µg/day; and
Km = 100 µg/ℓ.

8. Dietary uptake. Dietary uptake (U_D) is calculated as follows:

$$U_D = I_D \cdot A_D$$

where I_D (µg Pb/day) is the intake from dietary sources and A_D is the fractional gastrointestinal absorption of dietary lead. In the example presented in Table 4-1 for outdoor air lead levels of 0.25 $\mu g/m^3$, the calculation is as follows:

$$U_D = (29\ \mu g/day)(0.50) = 14.5\ \mu g/day$$

9. Outdoor soil lead. The model accepts monitoring data for lead in soil, or in the absence of data, estimates the geometric mean for dust and soil lead based on the following calculation:

$$[Pb]_S = 53 + 510 \cdot [Pb]_{Ao}$$

where $[Pb]_{DSo}$ are lead levels in soil (µg/g soil) and $[Pb]_{Ao}$ is lead concentration in outdoor air ($\mu g/m^3$). The values 53 and 510 are regression coefficients for monitoring data on air lead and soil lead (see Section 3.3.3.1. for further discussion). In the example presented in Table 4-1, the lead level in soil associated with an air lead of 0.25 $\mu g/m^3$ is calculated as follows:

$$53 + 510 \cdot 0.25\ \mu g/m^3 = 180\ (\mu g/m^3)$$

Confidence limits on the regression coefficients can also be incorporated into the calculation to estimate the upper and lower limits of the estimated lead levels in soil.

10. Indoor dust lead. The default calculation for indoor dust lead ($[Pb]_{Di}$) is similar to that for soil:

$$[Pb]_{Di} = 60 + 844 \cdot [Pb]_{Ao}$$

where $[Pb]_{Di}$ is the lead concentration in indoor dust (see Section 3.3.3.1. for further discussion).

11. Amount of dirt ingested. As discussed in Section 3.3.3.2., the amount of dirt (e.g., dust and soil) ingested on a daily basis can be expected to vary with age and tendency for soil pica. In the example presented in Table 4-1, a value of 0.20 mg/day is assumed for 2- to 3-year-old children.

12. Weighting factors for soil and indoor dust. The relative amounts of soil and indoor dust lead that are ingested depend on time spent indoors and outdoors and activity patterns within each environment. The model uses default weighting factors of 0.45 for soil and 0.55 for indoor dust.

13. Lead intake form ingesting soil and indoor dust. The combined lead intake from indoor dust and soil (I_DS) are calculated as follows:

$$I_{DS} = I_{SOIL} + I_{DUST}$$

where I_{SOIL} is the amount of soil lead ingested and I_{DUST} is the amount of indoor dust lead ingested each day.

Lead intake from soil (I_{SOIL}) and indoor dust (I_{DUST}) are calculated as follows:

$$I_{SOIL} = [Pb]SOIL \cdot D_{SING} \cdot (0.45)$$
$$I_{DUST} = [Pb]DUST \cdot D_{SING} \cdot (0.55)$$

where:

$[Pb]_{SOIL}$ = concentration of lead in soil (µg/g);
$[Pb]_{DUST}$ = concentration of lead in indoor dust (µg/g);
D_{SING} = amount of indoor dust and soil ingested (g/day);
0.55 = indoor dust weighting factor; and
0.45 = soil weighting factor.

In the example presented in Table 4-1, the calculations are as follows:

D_{SOIL} = 180 (µg/g) • 0.2 (g/day) • 0.45 = 16.2 (µg/day);
D_{DUST} = 271 (µg/g) • 0.2 (g/day) • 0.55 = 29.8 (µg/day);
I_{DS} = 16.2 (µg/day) + 29.8 (µg/day) = 46 (µg/day).

14. % Lead absorption from dirt. Quantitative information on absorption efficiency of lead from ingested dust and soil in humans is lacking. As discussed in Section 3.3.3.3., experiments with animals indicate that lead ingested in soil is absorbed less than lead in food; the results of in vitro studies indicate that lead is likely to be solubilized in human gastric fluids. To develop default values for the model, gastrointestinal absorption of solubilized lead is assumed to occur by non-saturable (passive) and saturable (active) mechanisms, similar to the assumption regarding the absorption of dietary lead (see Section 3.3.2). The absorption coefficient for soil lead (A_S) at any given dietary intake is, therefore, the sum of the passive absorption coefficient (A_{SP}) and the active absorption coefficient (A_{SA}), factored by the concentration for lead in the gastrointestinal tract and the apparent Km for active absorption, as follows:

$$A_S = A_{SP} + (A_{SA}/(1+([Pb]_{GI}/Km)^3))$$

where:

A_S = absorption coefficient for soil lead;
A_{SP} = coefficient for nonsaturable (passive) absorption;
A_{SA} = coefficient for saturable (active) absorption;
$[Pb]_{GI}$ = concentration of soil lead in the gastrointestinal tract (µg/ℓ); and
Km = apparent Km for saturable absorption (µg/ℓ).

The default values for 2- to 3-year-old children who are used in the model are as follows:

A_S = 0.3 for the default soil lead intake of 16.2 µg/day;
A_{SP} = 0.15;
A_{SA} = 0.15 for the soil lead intake of 16.2 µg/day;
$[Pb]_{GI}$ = 6 µg/ℓ for the default soil lead intake of 16.2 µg/day; and
Km = 100 µg/ℓ.

An identical computation strategy is used to calculate the absorption coefficient for indoor dust lead. Default values for all the variables used in the indoor dust lead calculations are identical to those for soil lead.

15. Lead uptake from dust and soil. Lead uptake from ingested dirt (U_{DS}) is calculated as follows:

$$U_{DS} = I_{DS} \cdot A_{DS}$$

where I_{DS} is the intake from dust and soil (µg/day) and A_{DS} is the fractional absorption. In the example presented in Table 4-1, the calculation for exposures to 0.25 µg/m^3 lead in air is as follows:

$$U_{DS} = (46 \text{ µg/day})(0.30) = 13.8 \text{ µg/day}$$

16. Drinking water lead (µg/ℓ). The default value for lead in drinking water is 9 µg/ℓ, which is the projected 1990-91 U.S. average concentration (Cohen, 1988a).

17. Drinking water intake. The default value for daily water intake in 2- to 3-year-old children is 0.52 ℓ/day.

18. Lead intake from drinking water. Lead intake from drinking water is calculated as follows:

$$I_W = [Pb]_W \cdot W_{ING}$$

where $[Pb]_W$ (µg/ℓ) is the average daily concentration of lead in drinking water and W_{ING} is the average amount of drinking water ingested.

In the example presented in Table 4-1, the calculation of lead intake from drinking water for exposures to 0.25 $\mu g/m^3$ air lead is as follows:

$$I_W = 9\ (\mu g/\ell) \cdot 0.52\ (\ell/day) = 4.6\ (\mu g/day).$$

19. % Gastrointestinal absorption of drinking water lead. The approach taken for calculating gastrointestinal absorption of drinking water lead is identical to that described previously for dietary lead. Absorption is assumed to occur by nonsaturable (passive) and saturable (active) mechanisms. The absorption coefficient for soil lead (A_S) at any given dietary intake is, therefore, the sum of the passive absorption coefficient (A_{SP}) and the active absorption coefficient (A_{SA}), factored by the concentration for lead in the gastrointestinal tract and the apparent Km for active absorption, as follows:

$$A_W = A_{WP} + (A_{WA}/(1+([Pb]_{GI}/Km)^3))$$

where:

A_W = absorption coefficient for drinking water lead;
A_{WP} = coefficient for nonsaturable (passive) absorption;
A_{WA} = coefficient for saturable (active) absorption;
$[Pb]_{GI}$ = concentration of lead in the gastrointestinal tract ($\mu g/\ell$); and
Km = apparent Km for saturable absorption ($\mu g/\ell$).

The default values for 2- to 3-year old children used in the model are as follows:

A_W = 0.5 for the default water lead intake of 4.4 μg/day;
A_{WP} = 0.15;
A_{WA} = 0.35 for the default intake of drinking water lead of 4.4 μg/day;
$[Pb]_{GI}$ = 2 $\mu g/\ell$ for the default water lead intake of 4.4 μg/day; and
Km = 100 $\mu g/\ell$.

20. Uptake of drinking water lead. Lead uptake from drinking water is calculated as follows:

$$U_W = I_W \cdot A_W$$

where IW (μg/day) is the intake from drinking water and A_W is the fractional absorption of ingested lead. In the example presented in Table 4-1, the calculation for exposure to 0.25 $\mu g/m^3$ air lead is as follows:

$$U_W = 4.6 \text{ (}\mu g/day\text{)} \cdot 0.5 = 2.3 \text{ (}\mu g/day\text{).}$$

21. Total lead uptake. Total lead uptake (U_T) is the sum of uptakes from breathing lead in air, diet, drinking water and dust/soil ingestion:

$$U_T = U_A + U_D + U_{DS} + U_W$$

In the example presented in Table 4-1, the total uptake associated with exposure to 0.25 $\mu g/m^3$ is calculated as follows:

$$U_T = 0.4 + 14.5 + 13.8 + 2.4 = 31 \text{ } \mu g/day$$

The calculation of media-specific uptakes presented in Table 4-1 shows that the largest contribution to total uptake in 2- to 3-year-old children is from dust, soil and diet. The contribution of inhaled airborne lead is relatively minor. Because of the relatively large contribution of dust and soil lead to total uptake, predictions of total uptake will be highly sensitive to changes in the values of input parameters related to dust and soil. For example, increasing the default value for gastrointestinal absorption of lead ingested in dust and soil from a value of 25-50% increases the predicted lower limit for total uptake from 8.1-12.1 μg/day. The default value for dietary lead absorption would have to increase to 72% to achieve a similar increase in total lead uptake. The results of studies on the gastrointestinal absorption of dietary lead in infants and young children suggest that it is improbable that the lower limit for gastrointestinal absorption of dietary lead is as high as 72%. However, 50% gastrointestinal absorption of lead in dust and soil is plausible, given the paucity of data concerning this parameter.

Predictions of blood lead are also sensitive to input data on lead concentration in soil and dust. For example, the use of site monitoring data for dust and soil lead, as opposed to default calculations based on air lead/dust and soil lead relationships, may have substantial quantitative impact on the prediction of total lead uptake. Another situation where the default calculations for air lead/soil dust lead relationships may not be appropriate are sites where a smelter once operated but has ceased operating. In this case, the air lead levels have dramatically decreased, but high soil lead concentrations may persist for some period of time, thereby heavily influencing the indoor dust concentrations. In this latter case, the equation used in the document would underestimate indoor dust concentrations.

4.1.2. Uptake of Lead from Ingested Paint. In the example presented in Table 4-1, it was assumed that the population of 2- to 3-year-old children was not exposed to lead from paint. However, ingestion of lead-based paint chips can be a quantitatively important source for lead uptake in children living or playing in areas in which decaying paint surfaces exist. Lead levels in the indoor dust of homes with lead paint can be 2000 μg/g (Hardy et al., 1971; Ter Haar and Aronow, 1974). A child that ingests 0.1 g of indoor dust each day would have a paint lead intake of 200 μg/day. Although not illustrated in the example, the model accepts input of age-specific estimates of intake from lead paint and incorporates these values in the calculation of total lead uptake. The computation strategy is similar to that used for calculating uptake from ingestion of soil and indoor dust lead. Nonsaturable and saturable absorption mechanisms are assumed to contribute to the uptake of lead solubilized from paint in the gastrointestinal tract.

The effect of lead paint ingestion on total lead uptake can be illustrated in the following example. Keeping all other parameters in Table 4-1 the same, an additional intake of 200 µg/day of paint lead in a 2- to 3-year-old child increases total lead uptake from 31-78 µg/day.

4.1.3. Uptake and Blood Lead Concentrations. Kneip et al. (1983) developed a biokinetic model for lead from data obtained in single dose and chronic lead exposure of infant and juvenile baboons. Estimated physiological and metabolic parameters for humans have been incorporated into the model for baboons to develop a predictive model for humans (Harley and Kneip, 1985). The resulting biokinetic model (Harley and Kneip, 1985) was selected by the Office of Air Quality Planning and Standards of U.S. EPA (1989a) to estimate age-specific blood lead levels associated with a given total lead uptake.

The Harley and Kneip (1985) model defines first-order rate constants for exchanges between blood and four physiological compartments that contain >95% of the lead body burden; bone, kidney, liver and gastrointestinal tract (Heard and Chamberlain, 1984). Rate constants for transfer of lead from the liver to the gastrointestinal tract and from blood to urine are also specified in the model (see Figure 2-1). Rate constants are adjusted for age-related changes in metabolism that affect the kinetics of distribution and excretion of lead in children. For example, uptake and elimination rate constants for bone are adjusted to account for expected changes in the rate of bone turn-over with age (Harley and Kneip, 1985). Similarly, age adjustments in excretion of lead in the urine, the transfer of lead from blood to liver and the fractional absorption from the gastrointestinal tract are incorporated into the model.

The model predicts levels of lead in blood, bone, kidney and liver associated with continuous lifetime uptake rates for children of various ages. While complete validation of the model in humans is not possible, comparisons can be made with the results of dietary studies in humans. Shown in Figure 4-1 are relationships between blood lead levels and lead uptake in 2-year-old children, as predicted by the biokinetic model of Harley and Kneip (1985) and from several studies of dietary lead uptake in infants and adults (Sherlock et al., 1982; Ryu et al., 1983; U.S. EPA, 1989a). The Harley and Kneip (1985) Model predicts lower blood lead levels than the uptake studies at low ($\leq$20 µg lead/day) lead uptakes. At higher uptakes ($\geq$20 µg/day), predictions are within the range determined for infants (Ryu et al., 1983) and higher than those for adults (Sherlock et al., 1982; Cools et al., 1976).

The Harley and Kneip (1985) Model has been extended in several directions, based on recent data, to develop the current version of the Uptake/Biokinetic Model. These extensions include the following:

1. additional compartmentation of the blood and bone lead pools (Marcus, 1985a,c);
2. kinetic non-linearity in the uptake of lead by red blood cells at high concentrations (Marcus,1985c);
3. transfer of lead from the mother to fetus.

The blood lead compartment is divided into plasma and red blood cell pools. The relationship between lead uptake and the concentration of lead in whole blood may be nonlinear at concentrations >20 µg/dl (Marcus, 1985a,c; Marcus and Schwartz, 1987). This may result from decreased binding of lead to erythrocytes at high lead concentrations (Barton, 1989).

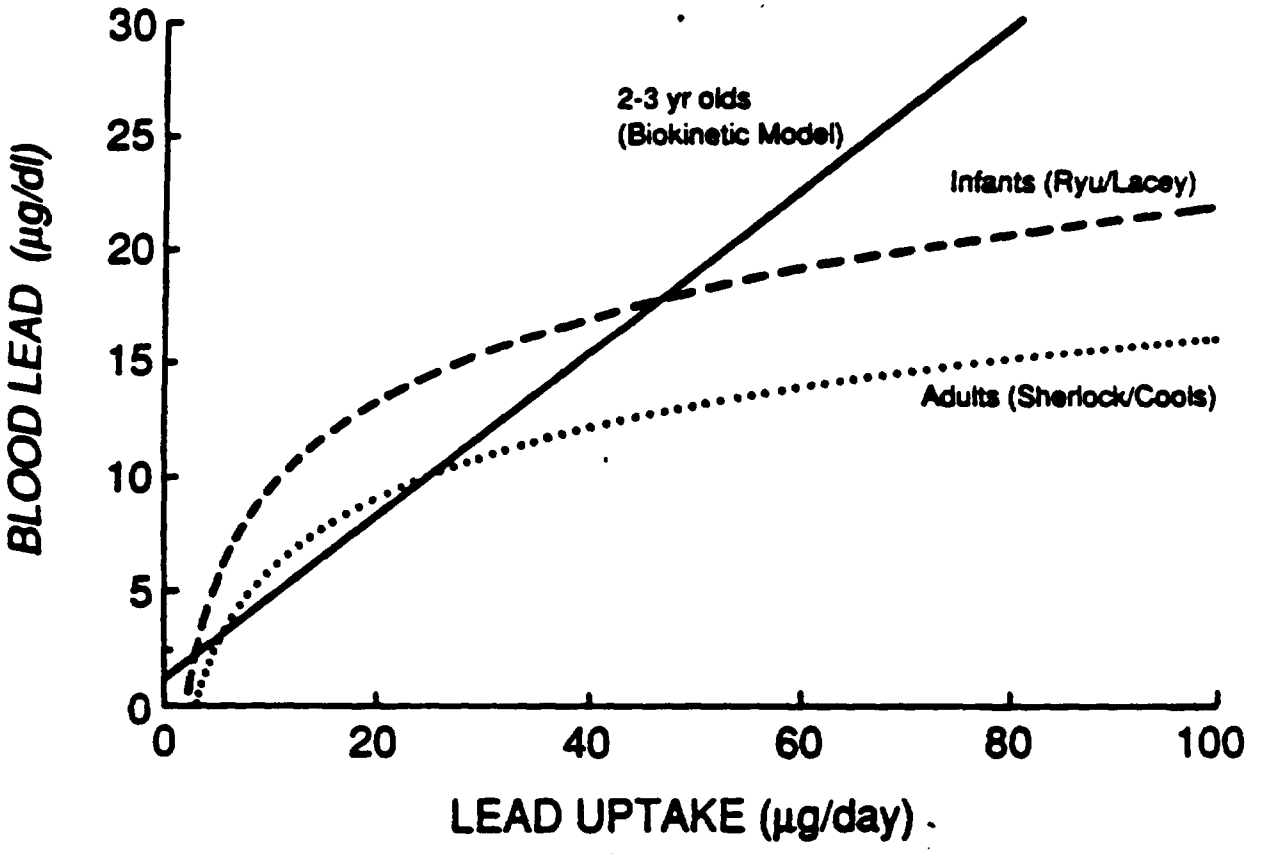


FIGURE 4-1

Summary of Relationships Between Daily Lead Uptake and Blood Lead for Infants (Ryu et al. 1983; Lacey et al., 1983), Adults (Sherlock et al., 1982; Cools et al., 1976), and 2- to 3-Year-Old Children Derived from the Harley and Kneip (1985) Biokinetic Model.

Source: U.S. EPA, 1989a

The bone compartment is divided into cortical and trabecular pools. Trabecular bone develops earlier and has a faster turnover (1-2 years) than cortical bone. In children, a large portion of the body burden of lead is in the more mobile trabecular bone pool.

The fetus receives lead from the mother in utero, and, thus, is born with a lead body burden that depends on that of the mother during pregnancy. The ratio of newborn lead levels to maternal blood lead is ≈0.8-0.9 (U.S, EPA, 1989a). A default ratio of 0.85 is used in the model to estimate newborn blood lead concentration. The current version of the model uses a default maternal blood lead level of 7.5 μg/dℓ; however, later versions will contain a maternal Uptake/Biokinetic Model in which maternal blood lead levels will be estimated from exposures to air, diet, drinking water and dust.

4.2. CALCULATIONS OF PROJECTED MEAN BLOOD LEAD DISTRIBUTIONS: LEAD UPTAKE LEVELS

The Uptake/Biokinetic Model predicts mean blood lead levels associated with defined multimedia exposure levels. However, to assess the risks associated with such exposures in a given population and evaluate potential effects of regulatory or abatement decisions, the frequency distribution for the population blood lead levels is a more useful parameter than population means. The fraction of the population with the highest blood lead levels will be the focus of regulatory and abatement decisions.

The distribution of blood lead levels is approximately log normal (U.S. EPA, 1986b) and, thus, is defined by its geometric mean and GSD. It is, therefore, possible to calculate the frequency distribution for blood lead levels, given a mean blood lead level and estimated GSD for the population. Estimated GSDs for blood lead levels in humans range from 1.3-1.4 (Tepper

and Levin, 1975; Azar et al., 1975; Billick et al., 1979). Schwartz (1985) estimated a GSD of 1.428 for young children after removing the variance in blood lead levels attributable to air lead exposure.

The OAQPS analyzed the NHANES II data on blood lead levels in adults; estimated GSDs are 1.34-1.39 for adult women and 1.37-1.40 for adult men (U.S. EPA, 1986b). The OAQPS (U.S. EPA, 1989a) also analyzed data from various studies of blood lead levels in children living near lead point sources (e.g., smoke stacks, smelters) (Baker et al., 1977; Yankel et al., 1977; Roels et al., 1980; CDC, 1983; Hartwell et al., 1983; Schwartz et al., 1986). The OAQPS concluded that

> "Until additional data are available, a range of 1.30-1.53 will therefore be assumed for children living near point sources as a reasonable range of GSD values (Roels et al., 1980; CDC, 1983), and the midpoint of 1.42 will be assumed as a reasonable best estimate."

Figures 4-2 and 4-3 show the frequency distribution for blood lead levels in 2- to 3-year-old children living near a lead point source with an air lead level of 0.25 $\mu g/m^3$, as predicted by the uptake/ biokinetic model and assuming a value of 1.42 for the GSD. Cumulative probability percentiles for the lower and upper limit estimates of total lead uptake are shown in Figure 4-2, and probability distribution for the upper limit estimates are shown in Figure 4-3. Assuming an upper limit total lead uptake, ≈9% of the 2-year-old population is predicted to have blood lead levels >10 μg/dℓ.

Several validation exercises were undertaken to test the performance of the Uptake/Biokinetic Model for predicting mean blood lead levels and distributions in human populations (U.S. EPA, 1989a). Results of the most extensive evaluation are shown in Figures 4-4 and 4-5. When site-specific data for air, dust and soil lead were used in the model, predicted and

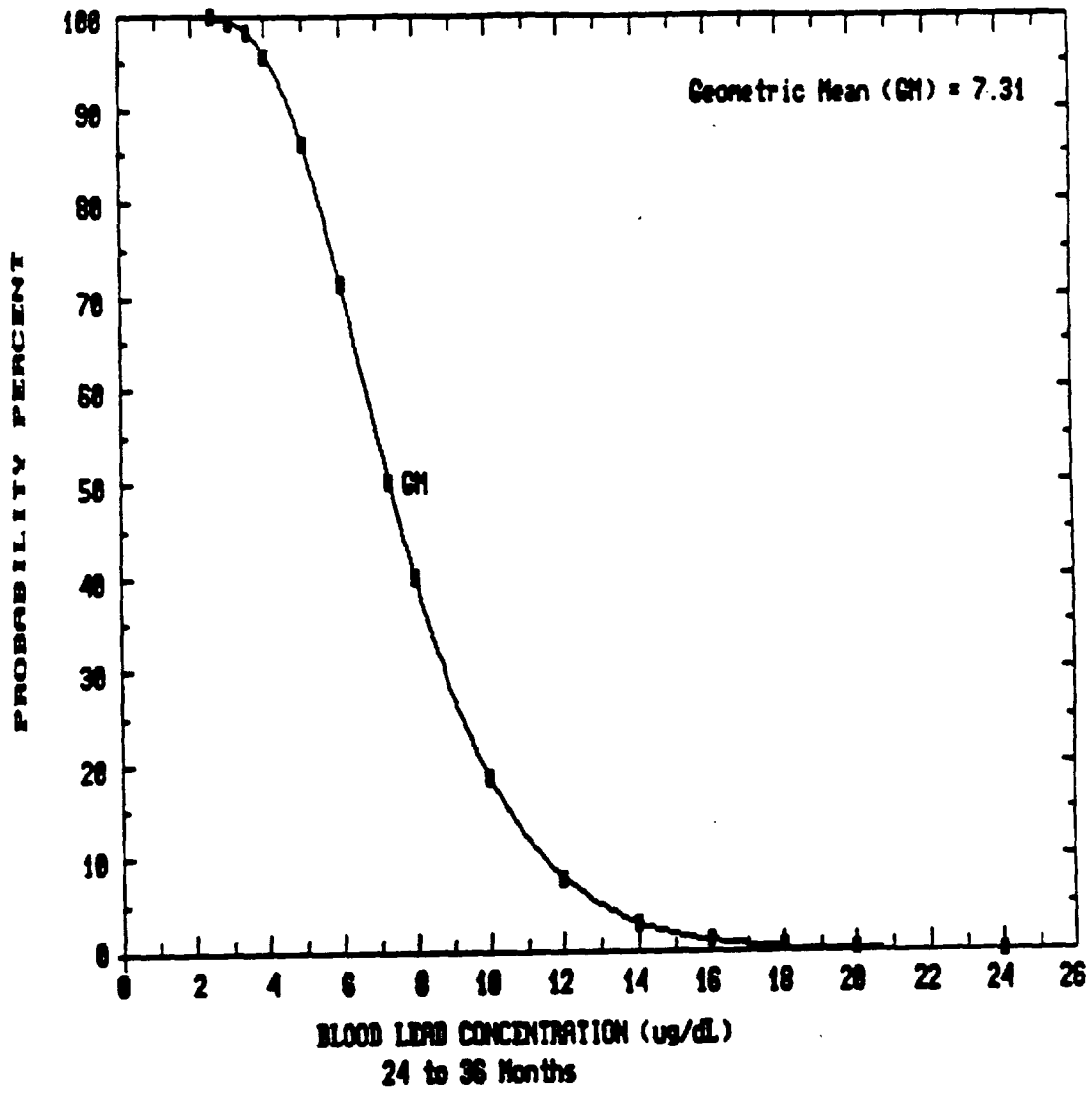


FIGURE 4-2

Probability Percentile of Blood Lead Levels in 2-Year-Old Children Living Near One or More Lead Point Sources and Not Affected by Blood Lead. Lead levels in air are assumed to be 0.25 $\mu g/m^3$. Lead uptakes were estimated from the uptake model (see Table 4-1).

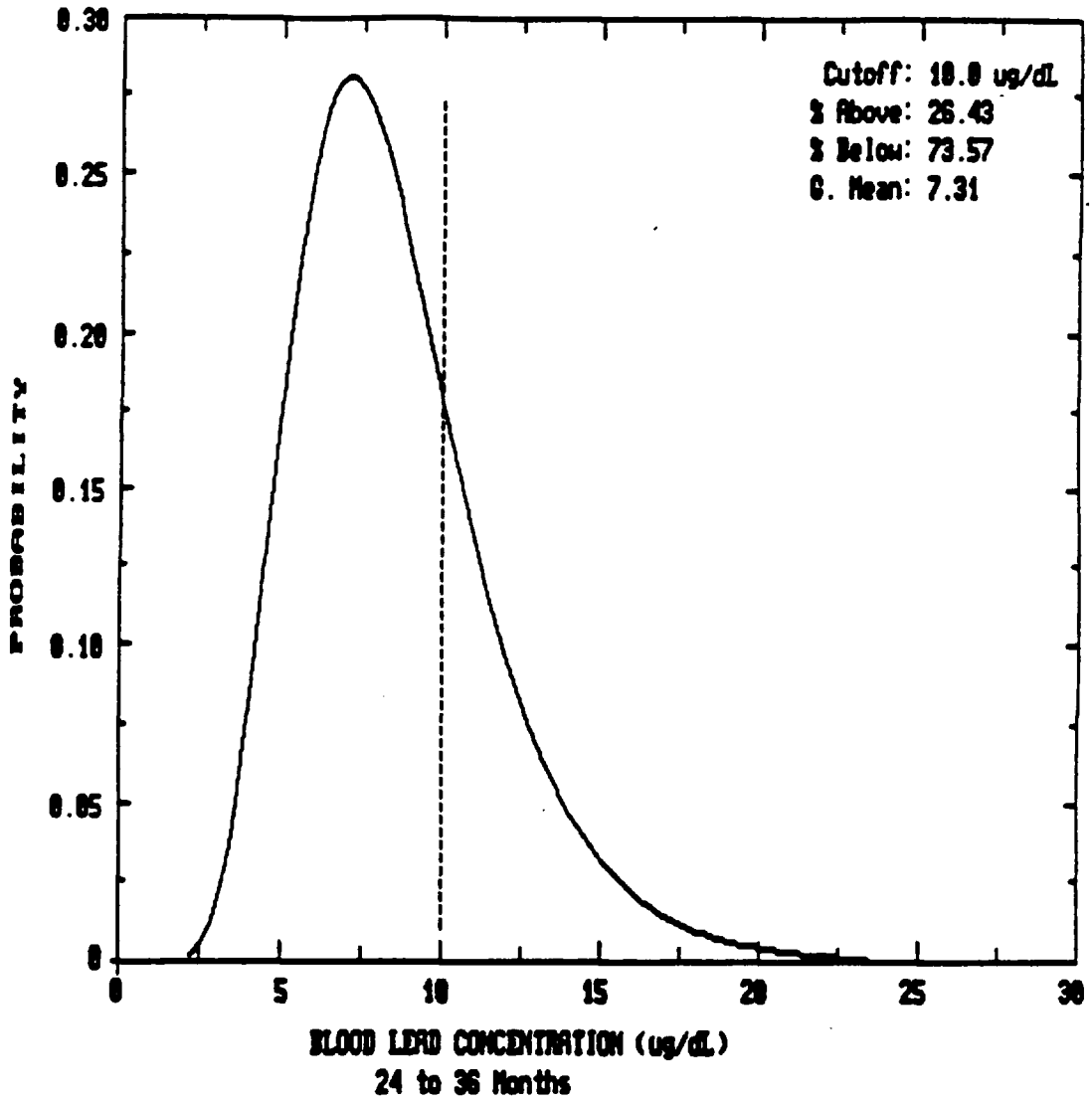


FIGURE 4-3

Probability Distribution of Blood Lead Levels in 2-Year-Old Children Living Near One or More Lead Point Sources and Not Affected by Blood Lead. Lead Levels in Air are Assumed to be 0.25 $\mu g/m^3$. A value of 1.42 is assumed for GSD of the predicted mean blood lead levels. The probability distribution is based on the predicted lead uptake (see Table 4-1).

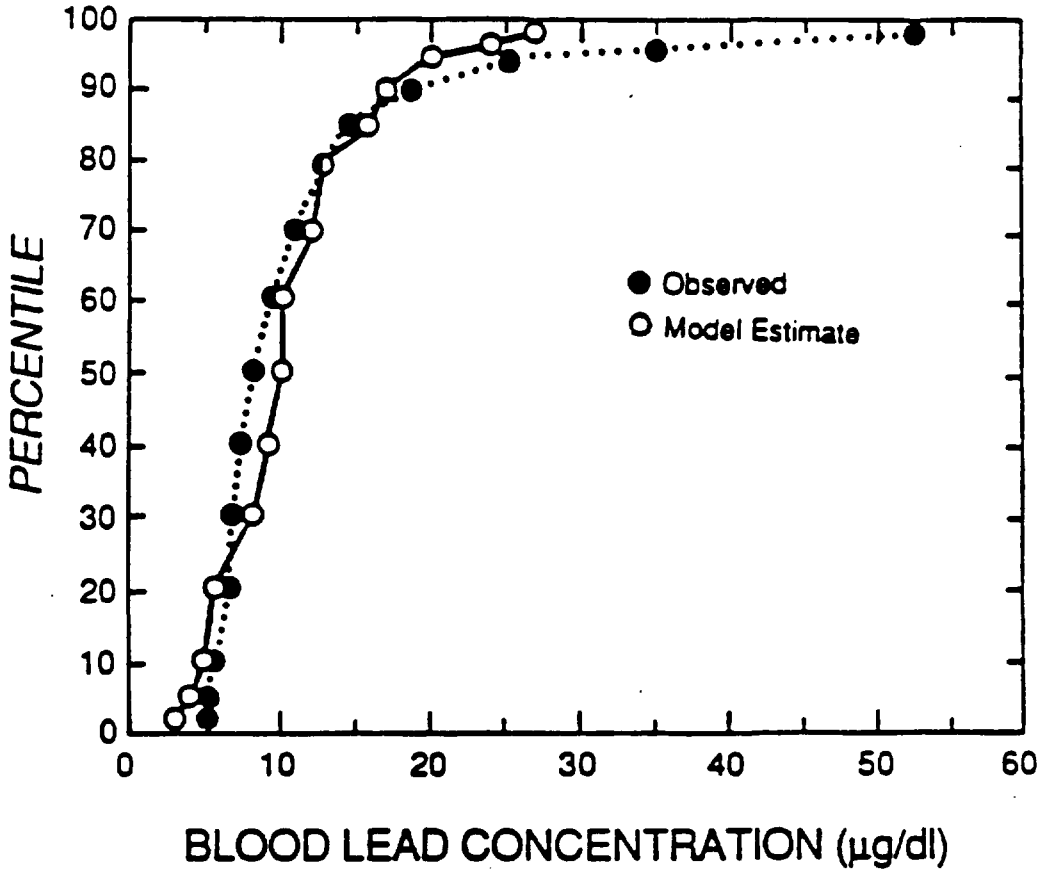


FIGURE 4-4

Comparison of Distribution of Measured Blood Lead Levels in Children, 1-5 Years of Age, Living Within 2.25 Miles of a Lead Smelter With Levels Predicted From the Uptake/Biokinetic Model. Measured dust and soil lead levels were included in the input parameters to the model.

Source: (As amended from) U.S. EPA, 1989a

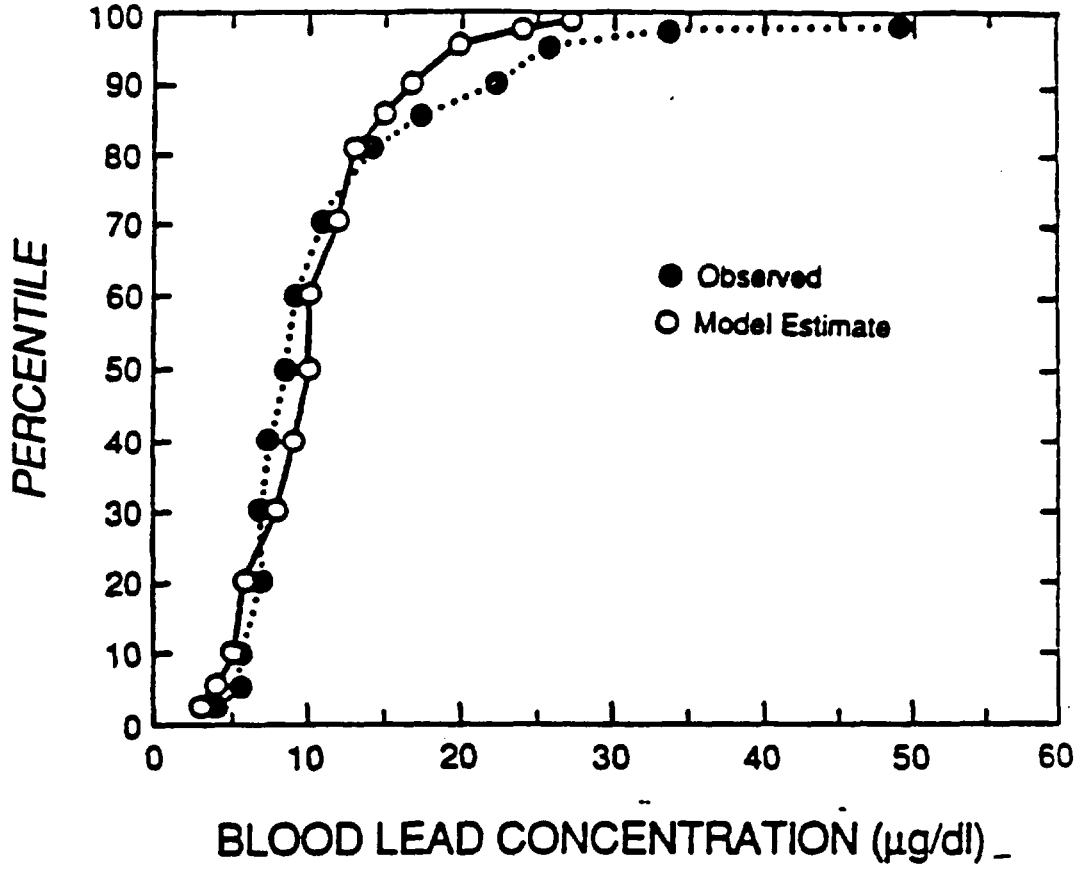


FIGURE 4-5

Comparison of Distribution of Measured Blood Lead Levels in Children, 1-5 Years of Age, Living Within 2.25 Miles of a Lead Smelter With Levels Predicted From the Uptake/Biokinetic Model. Dust and soil lead levels were estimated using default calculations.

Source: (As amended from) U.S. EPA, 1989a

observed mean blood lead levels and distributions were essentially identical up to the 90th percentile (Figure 4-4). Above the 90th percentile, the model slightly underpredicted blood lead levels. When default estimates of dust and soil lead were used in the model, predicted mean blood lead levels were within 2% of those observed; however, the model again slightly underpredicted blood lead levels at the highest percentile (Figure 4-5).

4.3. SUMMARY

An Uptake/Biokinetic Model that can be used to predict blood lead levels associated with multimedia exposures to lead in air, diet and dust/soil is described. The model consists of two components. The uptake model accepts monitoring data or estimated values for the levels of lead in each media and predicts a range of lead uptake rates that will result from exposure to each medium. The biokinetic model accepts estimates of total lead uptake and predicts mean levels of lead in blood, bone, liver and kidney for children of different ages. Mean lead levels can then be used to estimate frequency distributions for lead levels in populations of children, assuming a log normal distribution and a specified GSD. The results of several validation exercises indicate that the Uptake/Biokinetic Model accurately predicts mean blood lead levels associated with multimedia exposures in children; however, it may underpredict the highest level expected to occur in an exposed population.

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